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Management of Anaphylactic Reactions in Patients Suspected of Kounis Syndrome with Severe Cardiovascular Disorders

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Abstract
Kounis syndrome (KS) is a hypersensitivity coronary disorder induced by various conditions, drugs, environmental exposures, foods, and coronary stents. Allergic, hypersensitivity, anaphylactic and anaphylactoid reactions are associated with this syndrome. Vasospastic allergic angina, allergic myocardial infarction and stent thrombosis with occluding thrombus infiltrated by eosinophils and/or mast cells constitute are the three reported, so far, variants of this syndrome. Its etiology is continuously increasing. Kounis syndrome is a ubiquitous disease which represents a magnificent natural paradigm and nature's own experiment in a final trigger pathway implicated in cases of coronary artery spasm and plaque rupture. These cells are not only present in the culprit region before plaque erosion or rupture but they release their contents just before an actual coronary event. Therefore, awareness of etiology, epidemiology, pathogenesis, and clinical manifestations seems to be important for its prognosis, diagnosis, treatment, prevention

Keywords: Allergy; Anaphylaxis; Coronary Spam; Coronary Thrombosis; Kounis Syndrome; Stent Thrombosis

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Introduction

Kounis Syndrome is a disorder of coronary hypersensitivity caused by various conditions, drugs, environmental exposures, food and coronary stents (Now, 2016). Allergic reactions, hypersensitivity, anaphylaxis and anaphylactoid may be associated with this syndrome. The overall prevalence of KS in the United States is 1.1% among patients hospitalized for allergies/hypersensitivity/anaphylactic reactions, with a subsequent 7.0% rate of all-cause hospitalization mortality, according to a study published in *International Journal of Cardiology* (Liang, Zhao, Gao, Cao, & Wang, 2021)

Allergic vasopastic angina, allergic myocardial infarction, and stent-related thrombosis blockage infiltrated by eosinophils and/or mast cells are the three variants reported (Now, 2013). In addition to coronary arteries, it also affects the cerebral and mesenteric arteries. Its manifestations are widespread and its etiology is constantly increasing (Abdelghany, Subedi, Shah, & Kozman, 2017)

Kounis Syndrome is a disease in which the body itself as the last trigger pathway involved in the case of coronary arteries and plaque rupture. *Kounis Syndrome* Not a rare disease but a rarely diagnosed clinical entity that has revealed that the same mediators released from the same inflammatory cells also exist and in acute coronary events with non-allergic etiology (Cevik, Nugent, Shome, & Kounis, 2010). These cells are not only present in the causative area before plaque erosion or rupture but they release their contents before the actual coronary event. Therefore, an understanding of etiology, epidemiology, pathogenesis, and clinical manifestations is important for prognosis, diagnosis, treatment, prevention

Here we report a case of a 42-year-old male with ST-Elevation Myocardial Infarction (STEMI) and Anaphylactic Shock. This case report is made to improve understanding and ability to establish the diagnosis and proper management of *Kounis Syndrome*

Case Illustration

A 42-year-old man came in complaining of chest pain 4 hours before entering the hospital. The patient conveyed chest pain felt like pressure. Chest pain is felt in the left side of the chest. Complaints of chest pain accompanied by cold sweat. Complaints of chest pain are felt pain in the left hand. Complaints of chest pain are also recommended to penetrate to the back of the chest. Complaints of chest pain are not accompanied by pain in the teeth. The patient said that the patient also complained of shortness of breath. Complaints of shortness of breath are felt like heaviness in the chest and heaviness when breathing. Shortness of breath is not affected by a change in position. Shortness of breath is initially felt mildly, the day is getting more aggravating so that the patient can only be in bed. Complaints are also accompanied by occasional cough complaints without phlegm.

Patients also complain of itchy bodies. This itchy complaint is felt after the patient uses antibiotics. This complaint was felt 1 day before entering the hospital. Complaints are felt throughout the body accompanied by redness throughout the body. Complaints are felt increasingly aggravated but patients can still endure the itching. Complaints of

nasal congestion and fever are denied. Complaints at the time of defecation and urination are denied.

Two days before admission, the patient underwent cataract surgery at the Government Hospital. The patient said the operation went smoothly and there were no problems. After that, the patient returns home and the patient takes antibiotics. Complaints of itching in patients begin to be felt after patients consume antibiotics.

This history of allergies was first felt since the patient was in high school. Patients submit this complaint in the form of itching throughout the body accompanied by bumps on the arms, body and legs. This complaint is first felt when the patient consumes shrimp. After this happens, the patient says he rarely consumes shrimp. A history of other food allergies such as milk, eggs and other proteins is denied. The patient said that this was the first time the patient had an allergic reaction due to the drug.

History of patient diseases such as diabetes mellitus, hypertension, history of heart problems and kidney disorders does not exist. A history of other chronic diseases is denied. History of cancer or chronic diseases in the family such as diabetes (diabetes mellitus), hypertension, heart disease, kidney disease, asthma, or other chronic diseases are denied. Smoking history is recognized by the patient. The patient said he had been smoking since the age of 17 but had quit since 4 years ago. The patient is a private employee.

On physical examination, a general impression of severe illness with adequate nutritional status was found (BB 70 kg, TB 169 cm, BMI 21.30 kg / m^2). Compostmentic awareness, blood pressure 70/30 mmhg with dobutamine 10mcg/kgBB/min, pulse 113x/min, respiratory rate 21 x/min and axillary temperature 37▫C, VAS score 4/10. On examination of the eyes found conjunctiva is not anemic, sclera is not icteric. On examination of the neck found no enlarged lymph nodes, JVP PR 0 $cmH_{2O.\ On}$ physical examination of the lungs, it was found that the inspection looked symmetrical active. In tactile palpation of vocal fremitus there are no abnormalities, in percussion found sonor, auscultation found vesicular breath sounds, neither ronki nor whezing were found.

On physical examination of the heart the cordial limbus did not appear from the inspection, on palpation the citric ictus was found in the left anterior axillar of ICS VI, in percussion found the right heart boundary of 1 cm lateral parasternal right, and the left border of the heart in the left anterior axillar of ICS VI, in auscultation found tachycardia, normal heart sounds I and II, regular pulses and no murmurs were found. Abdominal examination was found not distention, normal intestinal noise, no tenderness, palpable liver, no enlarged lien, no ballottement found, tympanic percussion. In all four extremities it is palpable cold and there is no edema.

Figure 1. Photo of the patient.

Laboratory examination on April 20, 2022 WBC 25,3 x 10^3/µl, neutrophil 23,2 x 103/µl, limfosit 0,84 x 10^3/µl, Hb 16,9 gr/dl, MCV 90,2 fL, MCH 31,3 g/dL, PLT 274 x 10^3/ µl, SGOT 39 U/L, SGPT 35 U/L, BUN 10,70 mg/dL, Kreatinin 1,7 mg/dL, Glukosa darah sewaktu 184 mg/dl, PT 17 detik, APTT 29,4 detik, INR 1,21, TROP I 241,3 pg/mL, CKMB 51,6 U/L, Na 134 mmol/L, K 3.48 mmol/L, Hba1C 5 %. Analisa Gas Darah (AGD) pH 7.31, pCO2 41.0 mmHg, pO2 61.30 mmHg, BE -5.7 mmol/L, TCO2 21,90 mm/L, HCO3- 20,60 mmol/L, SO2c 88.%. total cholesterol 224 mg/dL, LDL cholesterol 172 mg/dL, HDL cholesterol 36 mg/dL, uric acid 8.33 mg/dL. In the laboratory examination of IgE a total of 486 IU / L was obtained

ECG images dated April 20, 2022 found HR 100-110 x/min, norm axis, P wave 0.08 sec, PR interval 0.16 sec, QRS complex 0.10 sec, R/S in V1 < 1, S in V2 + R in V5 < 35 mm, ST – T change (+) there is ST elevation V1-V6. Effect: rhythm sinus with anterior SEMI.

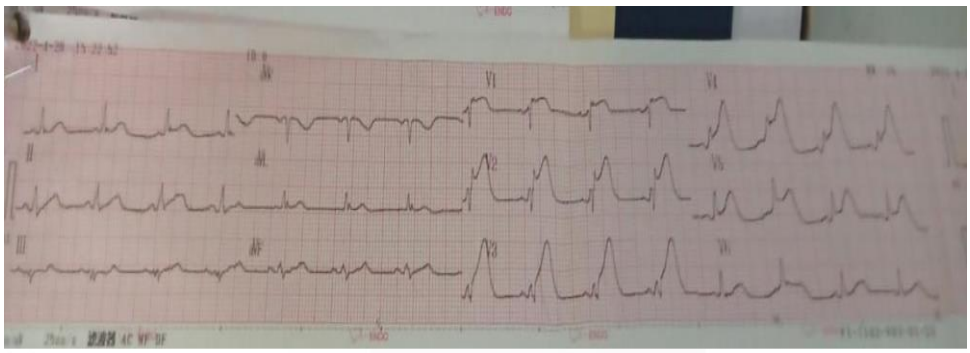


Figure 2. ECG of the patient.

On examination of Thorax AP on April 20, 2022, it was found that the tissuedid not appear abnormalities. The bones did not appear abnormalities. The left right pleural sinus

is sharp. The right and left diaphragm is normal. Large cast and normal effect form, CTR 55%. Trachea is located in the middle, airway patent. Pulmo does not appear consolidated/nodule. Increased vascular smears, cephalization (+). With the impression of cast does not appear abnormality and congestive pulmonum.

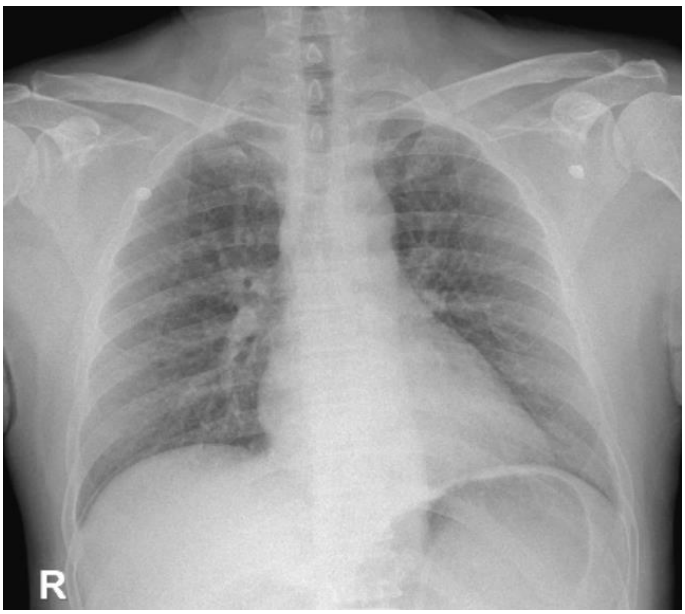
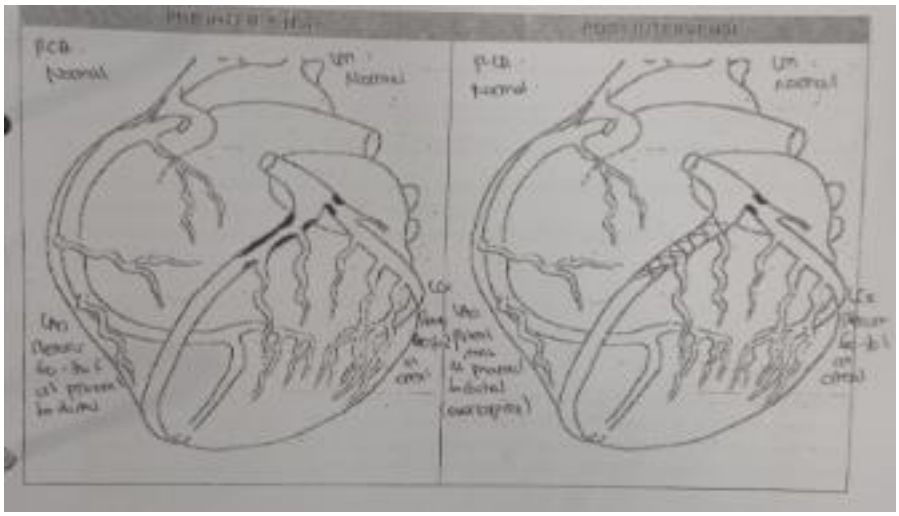


Figure 3. Thorax patient photo .

After being diagnosed with Anterior SEMI, patients are treated with primary PCI with Killip IV anterior STEMI results, Onset 4 hour, TIMI/14, EF BP 50%, RWMA (+). Shock Anafilaktik. 1. *Uncomplicated puncture of right radial artery with modified seldinger technique with* Lidocaine 2% local anesthesia. Heparin 5000 IU. Nitrate 300 mcg. 2. *Canulation using guiding catheter TIG Optitorque 3.5/5 F and Terumo wire 0.035"/180 cm. 3. L/RCA-graphy: LM : Normal LAD: Stenosis 60-70% at proximal to distal. LCx : Stenosis 70-80% at osteal. RCA: Normal 4. PCI at LAD Canulation at proximal LAD with catheter using JL 3.5/6F. Wiring into distal LAD using Asahi Sion Blue 0.014"/180 cm. Stenting using Resolute Integrity 2.75 mm x 30 mm into proximal until mid LAD deployed at 9 atm/9". Stenting again using Resolute Integrity 2.75 mm x 30 mm into mid into distal deployed at 10 atm/11". Angiography show TIMI 3 flow at distal LAD. Patient was stable in return. Conclusion: CAD 2 VD. Post successful Primary PCI with 2 DES at proximal to distal LAD (Overlapping stent) Suggestion Elective PCI at LCX*.



Gambar 4. *Primary PCI*

Patients diagnosed anaphylactic shock, STEMI anterior Killip IV with onset 4 hours, TIMI score 6/14, EF fraction 47%, RWMA (+), CAD 2VD, OD pseudophakia post pacho + IOL. Patients received nasal cannula oxygen therapy 3 liters per minute, IVFD NaCl 0.9% loading 500 ml in the first 1 hour, followed by 20 drops per minute, drip vascon with a start of 0.1 mcg / kg body weight, dobutamine starting 5 mcg / kg body weight, clopidogrel 300 mg, aspilet 160 mg. In addition, patients also received epinephrine 0.3 mg intramuscularly, hydrocortisone 200 mg followed by 100 mg every 8 hours intravenously and diphenhydramine 10 mg intramuscularly followed by 10 mg cetirizine every 24 hours intraorally. Patients were also given a shrimp- and egg-white-free diet of 1900 kcal/day. The patient will be treated elective PCI through cardiac poly. Monitoring: complaints, vital signs, urine production / 24 hours (fluid balance), and watch for signs of anaphylactic reactions.

On the third day of treatment, the patient was declared improved and the patient was discharged with a control note back to the heart poly and internal medicine poly of the allergy immunology section.

Discussion

Kounis Syndrome An acute coronary syndrome includes coronary seizures, acute, myocardial infarction, and stent thrombosis, with conditions associated with mast cell and platelet activation and involving interrelated and interacting inflammatory cells, such as macrophages and T lymphocytes, in the setting of allergies or hypersensitivity and anaphylaxis or anaphylactoid (Fassio et al., 2016). This syndrome is caused by inflammatory mediators such as histamine, platelet-activating factor, arachidonic acid products, neutral proteases and various cytokines and chemokines released during allergic reaction activation processes. Although mast cells constitute a minority in this inflammatory cascade, they greatly influence the inflammatory process. All these inflammatory cells participate this inflammatory process by activating each other through various signals and becoming activated (Rodrigues, Coelho, & Granja, 2013)

For example, mast cells can activate macrophages and can increase T cell activation. Induced macrophage proteins can activate mast cells, whereas CD169 macrophages activate CD8 T cells (Kounis, Koniari, & de Gregorio, 2021). T cells can mediate mast cell activation and proliferation and regulate macrophage activity. Recent research suggests that syndromes like Kounis's can affect the mesenteric and cerebral arteries (Kouni, Patsour, Graps, & Hahal, 2015). The coronary arteries, heart and entire arteries of the system appear to be susceptible to allergies, hypersensitivity, anaphylaxis and anaphylactoid and should be alert to the consequences

Causes for occurrence *Kounis syndrome* This is quite a lot. This includes certain types of food, various medications, environmental exposures and some conditions (Brancaccio et al., 2024). Latest for *Kounis syndrome* Food-induced are fish, shelves, fruits, vegetables and canned food. Some etiologies are described through table 1 below

Table 1

Grass cutting *Hymenoptera stings*

Medicinal drugs	Condition	Food	Milieu
- Analgetic (aspirin, dipyrone) - Anesthesia (etomidate, isoflurane, midazolam, propofol, remifentanil, rocuronium bromide, succinylcholine, suxamethonium, trimethaphan) - Antibiotic (ampicillin, ampicillin/sulbactam, amoxicillin, amikacin, cefazolin, cefoxitin, cefuroxime, cephalin, cinoxacin, lincomycin, penicillin, sulbactam/etoperidone, piperacillin/tazobactam, trimethoprim sulfamethoxazole, sulperazon, vancomycin) - Anticoagulants (heparin, lepirudin) - Anti-neoplastic (5-fluorouracil, capecitabine, carboplatin, Deniliquin, interferons, paclitaxel, vinca alkaloids) - Media contras (Iohexone, lox agate, meglumine diatrizoate, sodium indigotindisulfonate) - Glucocorticoids (betamethasone, hydrocortisone) - Nonsteroidal anti-inflammatory drugs (alclofenac, diclofenac, naproxen) - Proton pump inhibitors (lansoprazole) - Skin disinfectants (chlorhexidine, povidone iodine) - Thrombolytics (streptokinase, tissue plasminogen activator, urokinase) - etc. (allopurinol, bupropion, clopidogrel, dextran, enalapril, esmolol, fructose, gelofusin, insulin, iodine, iron, losartan, protamine, tetanus antitoxin, graphene, mesalamine)	- Angioedema - Anisakiasis - Bronchial asthma - Churg-Strauss syndrome - Exercise-induced anaphylaxis - Food allergy - Hay fever - Idiopathic - Anaphylaxis - Intracoronary stenting - Masto cytosis - Nicotine - Scombroid syndrome - Serum sickness - Skin itching - Stents (bare metal, drug eluting)	- Actinidia chinensis - Canned food (tuna) - Fish - Fruits - Mushroom poisoning (Coreopsis armamentaria) - Shellfish - Vegetables - Tomato salad	- Grass cutting - Hymenoptera stings - Jellyfish stings - Latex contact - Millet allergy - Poison ivy - Scorpion sting - Viper venom - Metals

In this patient, the cause of the anaphylactic reaction is the use of antibiotics. This patient experiences a rapid anaphylactic reaction. This condition is exacerbated by the complication of anaphylaxis, namely *coronary acute syndrome*.

Pathophysiology of the disease kounis syndrome

The course of the disease in patients experiencing *Kounis syndrome*, The main inflammatory cells involved in the development of this condition are mast cells that interact with macrophages and T lymphocytes through multidirectional stimuli. Mast cells enter the circulation from the bone marrow as precursors of mononuclear cells and circulate as precursors of mast cells (Alagesan et al., 2023)

On its surface receptors for stem cell factors. Stem cell factors are cytokines that are important for mast cell growth, differentiation, development, proliferation, survival, adhesion, and return. The cells enter all human tissues even into brain tissues that do not suffer from allergic reactions because IgE antibodies cannot cross the blood-brain barrier. In contrast, basophils mature in the bone marrow from precursor granulocytes and enter the circulation as mature cells and do not enter the tissues, during the later stages of an allergic reaction.

Leukotrienes are potent vasoconstrictors and their biosynthesis increases in the acute phase of unstable angina. Thromboxane is a strong mediator of platelet aggregation with vasoconstrictive properties and PAF, myocardial ischemia, acts as a proadhesive signaling molecule through activation of leukocytes and platelets to release leukotrienes or as a direct vasoconstrictor (THE WRESTLER, Khusna, & Septiana, 2021). All these newly formed and newly synthesized inflammatory mediators released locally and flowing into the systemic circulation can cause coronary artery spasm that can develop into acute or direct coronary myocardial damage, thrombosis, which is the main clinical manifestation of Kounis syndrome (Fourie, 2016)

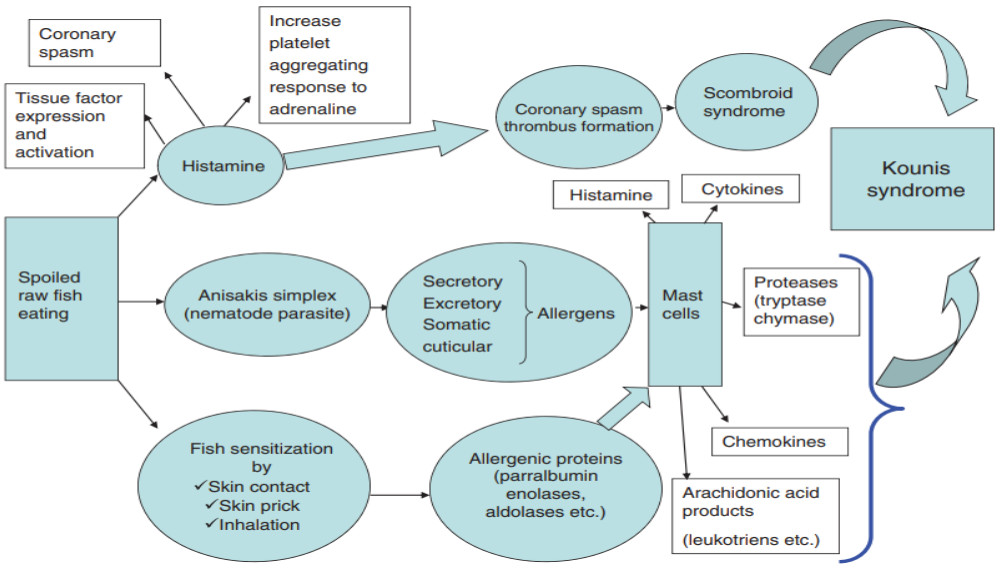


Figure 5. Pathophysiology of Kounis Syndrome[5]

Clinical presentation

The main clinical symptoms and signs of Kounis syndrome are always associated with subclinical, clinical, acute or chronic allergic reactions accompanied by cardiac symptoms. Various electrocardiographic changes ranging from elevation or depression of the ST segment to degrees of heart block and cardiac arrhythmias resembling digitalis intoxication are always associated with cardiac symptoms and signs (Table 2). A high index of suspicion regarding this syndrome is very important (Nikolaidis, Kounis, & Gradman, 2002)

Table 2

Coronary angiography (spasm, thrombosis)

symptom	Sign	ECG overview	Laboratory
- Acute chest pain - Chest discomfort when swallowing - Dyspnea -Faint -Headache -Malaise -Nauseous - Pruritus - Itching of the skin -Vomit	- Bradycardia - *Cardiorespiratory arrest* Cold extremity Sweat Hypotensive Pallor Palpitations Skin rash - Takikardia	- Atrial fibrillation - Bigeminal rhythm - Heart block - Nodal rhythm - Sinus bradycardia - Sinus tachycardia - ST segment depression or elevation - T-wave flattening dan or inversion - Prolong QRS complex - Prolong QT segment - Ventricular ectopic - Ventricular fibrillation	- Coronary angiography (spasm, thrombosis) - Increased *cardiac enzymes* (CPK-MB) - Increased Troponin - Cardiomegaly pada chest X-ray - Dilates *cardiac chambers* at echogram - Eosinophil and/or or cell mast at *coronary biopsy* - MRI: subendocardial gadolinium concentration - SPECT: ischemia

Diagnosis

Diagnosis *Kounis syndrome* Based on clinical symptoms, symptoms and signs as well as laboratory evidence, electrocardiography, echocardiography and angiography. These various findings may accompany allergies which helps in putting the correct diagnosis. Modern tools such as magnetic resonance imaging of the heart and myocardial scintigraphy have helped to confirm the diagnosis. A high index of suspicion is very important. Patients with systemic disease allergic reactions associated with clinical findings, electrocardiography and laboratory acute myocardial ischemia should be suspected (Table 2) (Nikolaidis et al., 2002)

Measuring serum tryptase, histamine, cardiac enzymes and cardiac troponin is helpful in diagnosis. Triptase, like other inflammatory mediators, is short-lived and has a half-life effect of about 90 minutes. The best time for the first specimen seems to be half an hour after the initial symptoms and 30 minutes after it for the next 2 hours. It should be pointed out that elevated levels of tryptase may be present in circulation for several hours. Postmortem aortic tryptase measurement can be as beneficial as soon as possible after death in cases of *Kounis syndrome*.

The release of histamine from mast cells is rapid and short-lived and circulates only about 8 minutes after the allergic event, therefore blood samples should be collected

immediately after the onset of chest pain and before administration of analgesics, especially morphine. Heart enzymes such as CK and specifically CK-MB are beneficial in diagnosing heart damage associated with allergic reactions or anaphylaxis. Cardiac troponin measurement is strongly recommended in all patients admitted to the emergency department with acute allergic reactions in order to timely diagnose and appropriately manage potential cardiac injury manifesting as *Kounis syndrome* or *Takotsubo cardiomiopathy*.

Echocardiography and coronary angiography are needed in diagnosing heart wall abnormalities, including: *Takotsubo cardiomiopathy* and describes coronary anatomy in the case of *Kounis syndrome*. New techniques such as thallium-201 single photon emission computer tomography (SPECT) and 125I-15-(p-iodophenyl)-3-(R,S) methylpentadecanoic acid (BMIPP) SPECT have been used. Magnetic dynamic cardiac resonance imaging (MRI) is also a reliable tool for assessing heart involvement in *Kounis syndrome*. On this MRI, contrast shows normal washout in the area of the subendocardial lesion in patients with *Kounis syndrome* type I (Nikolaidis et al., 2002)

In patients obtained symptoms of dyspnea, nausea, vomiting, itching of the skin, chest pain, and shortness of breath. On physical examination, hypotension is found, skin rash, cold extremities. In the ECG image, there is an ECG ST Elevation image on V1-V6 with the impression of Anterior SEMI. In laboratory examinations, an increase in CKMB and Troponin I was obtained.

Governance

Systemic allergic responses caused by inflammatory mediators should be controlled early in the management of these patients. However, therapeutic management *Kounis syndrome* It is challenging to treat both heart symptoms and allergies at the same time. Treatment given to treat cardiac manifestations may worsen allergies and medications given to treat allergic symptoms may worsen heart function (Vigorito, Poto, PicoTTi, Triggiani, & Marone, 1986), (Caglar, Caglar, Coskun, Ugurlucan, & Okcun, 2011)

In patients with type I variants, allergy treatment alone can relieve symptoms. The use of intravenous corticosteroids such as hydrocortisone at a dose of 1-2 mg / kg / day and H1 and H2 antihistamines such as diphenhydramine at a dose of 1-2 mg / kg and ranitidine at a dose of 1 mg / kg is sufficient. Administration of vasodilators such as calcium and nitrate channel blockers can eliminate vasospasm-induced hypersensitivity. Nitroglycerin can cause hypotension and tachycardia which can further complicate anaphylactic reactions. Most patients with this reaction have tolerated oral and sublingual nitroglycerin. Therefore, intravenous or sublingual use of nitroglycerin appears to be reasonable and safe in patients with *Kounis syndrome* If blood pressure is not disturbed. Bolus administration of antihistamines may provoke hypotension and disrupt coronary flow

In patients with type II variants, treatment should be started with an acute coronary event protocol along with corticosteroids and antihistamines. Vasodilators such as nitrates and calcium inhibitors are administered. Beta-blockers can make coronary spasms worse

due to adrenergic action that receptors do not fight. Epinephrine which is the drug of choice and can be lifesaving in anaphylaxis, but in *kounis syndrome* aggravates ischemia and worsens coronary vasospasm. In difficult cases, intravenous epinephrine is preferred to be administered intramuscularly because it has a faster onset of action and a more sustained rate compared to the subcutaneous route (recommended intramuscular dose of 0.2-0.5 mg [1:1000]).

In patients with a previous history of coronary heart disease, who receive b-blockers, epinephrine may not be effective. In this case glucagon infusion (1–5 mg, intravenously for 5 minutes, followed by infusion 5–15 g/min) may be used for patients who are already beta-blockers or receiving them during the management of acute coronary syndrome. Metoxamine, a powerful alpha agonist, may also be considered in patients who do not respond to epinephrine. Such opiates such as morphine, codeine and meperidine given to relieve acute chest pain should be administered with extreme caution, as they can induce massive mast cell degranulation and worsen allergic reactions

In patients with the current type III variant, myocardial infarction protocol along with urgent aspiration of intrastent thrombus followed by histological examination, examination of the aspirated material and staining for eosinophils (hematoxilin and eosin) and mast cells (Giemsa) should be performed. In patients who have allergies with symptoms after implantation of antihistamine stents along with corticosteroids and mast cell stabilizers can relieve symptoms. When symptoms persist, identification of the culprit cause with skin tests should be ascertained and desensitization measures should be applied. If these steps fail, stent extraction seems unavoidable

Conclusion

Cases have been reported of a 42-year-old man with anaphylactic shock, Anterior SEMI, CAD 2VD and Pseodufakia OD. In these patients an anterior STEMI occurs resulting from an anaphylactic reaction. In patients have been treated for anaphylactic shock and management of acute coronary syndrome with Primary PCI. The definitive diagnosis in *Kounis syndrome* patients is the discovery of eosinophils on blood vessel biopsy.

Kounis syndrome is a complex acute coronary disease syndrome that requires treatment and prompt decisions. After relieving acute events, a complete cardiological examination, including an ECG of 12 leads, echocardiogram, and modification of cardiac risk factors, is required. An allergy work-up should follow to include other assessments of allergies to food, insect stings, drugs, and other environmental agents. Skin and food tests may be useful in identifying the cause

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