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Kounis syndrome risk factors, pathophysiology, and management

Abstract

The combination of acute coronary syndromes, illnesses associated with mast cell activation, interconnected and interacting inflammatory cells, allergic or hypersensitive reactions, and anaphylactic or anaphylactoid episodes is known as the Kounis syndrome. Non-steroidal anti-inflammatory drugs (such as ibuprofen, alclofenac, diclofenac, and naproxen) are the most frequently observed medications that cause Kounis syndrome, followed by antibiotics like ampicillin, azithromycin, ampicillin/sulfactam, amoxicillin, amikacin, cefazolin, cefoxitin, cefuroxime, cephradine, cinoxacin, lincomycin, penicillin, cefopera (5-fluorouracil, capecitabine, carboplatin, denileukin, interferons, paclitaxel, vinca alkaloids). There are three main types of Kounis syndrome: type 1 is allergic vasospastic angina, which is caused by endothelial dysfunction and is one of the causes of non-obstructive myocardial infarction; type 2 is allergic myocardial infarction; and type 3 is allergic stent thrombosis with an occluding thrombus (subtype a) or stent restenosis (subtype b). The first step in treating Kounis syndrome is to stop the allergic reaction, then use medicinal or interventional methods to stabilize the coronary arteries. Strong immunosuppressive and anti-inflammatory drugs, corticosteroids play a significant part in the management of allergic responses. Kounis syndrome is treated with intravenous corticosteroids, such as hydrocortisone, at a dosage of 5 mg/kg/day.

Keywords: kounis syndrome, management, pathophysiology, risk factors

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Abbreviations: ACS, acute coronary syndrome; CD95, cluster of differentiation-95; ECG, electrocardiographic; KS, kounis syndrome; MI, myocardial infraction; MMP, metalloproteinases; MRGPRX2, mas-related g protein-coupled receptor X2; PR, pulse rate; ST, serum troponin; SARS-COV-2, severe acute respiratory syndrome-corona virus-2

Introduction

Kounis syndrome is defined as the co-occurrence of acute coronary syndrome, mast-cell activation, and platelet activation when hypersensitivity, allergy, or anaphylactic offenses are present.[1] The KS is an allergic acute coronary syndrome caused by an anaphylactic, anaphylactoid, allergic, or hypersensitive offense (clinical circumstances characterised by mast cells activation with large histamine release).[2] It includes coronary spasm, sudden myocardial infarction, and stent thrombosis. Recently, the term «Kounis syndrome» has been used to describe allergic angina syndrome (also known as allergic myocardial infarction or allergic angina pectoris), which includes the production of inflammatory cytokines through mast cell activation and results in coronary artery vasospasm and/or atheromatous plaque erosion or rupture.[3] Kounis syndromes are widespread illnesses that can affect patients of all ages, from children to the elderly. They have a wide range of accelerating causes, expanding clinical presentations, and a wide range of mast cell activation abnormalities.[4]

Risk factors

Prior allergy history, hypertension, smoking, diabetes, and hyperlipidemia are risk factors for KS. Kounis syndrome has been linked to a number of triggers, including certain meals, medications, environmental factors, medical problems, and coronary stents. Any chemical, illness, or environmental exposure that might stimulate the development of IgE antibodies could be a potential cause of Kounis syndrome. Fruits, vegetables, fish, bonsai, shrimp, and mushrooms are possible food triggers.Non-steroidal anti-inflammatory drugs (such as ibuprofen, alclofenac, diclofenac, and naproxen) are the most frequently observed medications, followed by antibiotics like ampicillin, ampicillin/sulfactam, azithromycin, amoxicillin, amikacin, cefazolin, cefoxitin, cefuroxime, cephradine, cinoxacin, lincomycin, penicillin, cefoperazone/sulbact (5-fluorouracil, capecitabine, carboplatin, denileukin, interferons, paclitaxel, vinca alkaloids). Other pharmaceutical agents such as anesthetics (etomidate, isoflurane, midazolam, propofol, remifentanil, rocuronium bromide, succinylcholine, suxamethonium, trimethaphan), antiviral, analgesics (acetaminophen, aspirin, dipyridamole), antifungal, glucocorticoids (betamethasone, hydrocortisone), inactivated SARS-COV-2 Vaccine example cause type I kounis syndrome, COVID-19 infection, antihistamines, proton pump inhibitors (lansoprazole), antiacids, antihypertensives, antiplatelets, anticoagulants (heparin, lepirudin), thrombolytics (streptokinase, tissue plasminogen activator urokinase), sympathomimetics, skin disinfectants (chlorhexidine, povidone iodine), volume expanders, neuro-muscular blockers, skin antiseptics, contrast media (gadolinium, Iohexone, loxagate, meglumine diatrizoate, sodium indigotindisulfonate), and oral contraceptives can also serve as triggers. Kounis syndrome can also be brought on by environmental factors such grass, poison ivy, metals, latex, dialysate, nicotine, and bites or stings from Hymenoptera, which includes stinging hornets and bees, black widow spiders, snakes, scorpions, or jellyfish. Other medical diseases, including idiophatic anaphylaxis, exercise-induced anaphylaxis, mastocytosis, serum sickness, Churg Strauss syndrome, angioedema, asthma, scombroid syndrome, or anisakiasis, have been linked to Kounis syndrome.[5–14]

Pathophysiology

Mast cell activation and degranulation, which cause the release of powerful inflammatory mediators, is the root of three distinct pathophysiologic processes that cause Kounis syndrome. Kounis syndrome presently has three recognized subtypes. Patients who have healthy coronary arteries and no risk factors for coronary artery disease get the type 1 variation. Acute allergic reactions can result in

a progressive spasm of the coronary arteries that leads to myocardial infarction (MI). Patients with pre-existing quiescent atheromatous disease who experience an allergy irritant may experience an acute plaque rupture that manifests as a MI. Thrombosis in prior coronary artery stents or type III stent thrombosis (subtype IIIa) or stent restenosis (subtype IIIb) after an allergic response are examples of type 3 variants.[15,16] Mast cells that interact with macrophages and T lymphocytes are the earliest inflammatory cells involved in the development of Kounis syndrome. It results in mast cell degranulation and the release of inflammatory mediators such histamine, neutral proteases like chymase, tryptase, and heparin, as well as increased leukotriene synthesis. Complements are activated during an anaphylactic response along with the production of anaphylatoxin. On the surface of cardiac mast cells are their particular receptors. Mast cell degranulation, the last stage of these processes, causes the release of histamine, tryptase, and chymase as well as the production of prostaglandin and leukotriene. Atheromatic alterations in artery walls result in an increase in histamine concentration.Additionally, the atheromatous plaque's connective tissue is deteriorated by metalloproteinases (MMP: MMP-1, MMP-3, and MMP-9) that are activated by proteases (Tryptase, Chymase, and Cathepsin-D) released by excited mast cells. The plaque becomes more susceptible to rupture, making it vulnerable.[17–19] Non-IgE antigens, such as those that bind to neurotensin and MRGPRX2 receptors, can also cause the discharge of the contents of mast cells in addition to particular IgE antigens. Mast cell activation occurs via four primary routes, including I) the cross-linking of allergen-specific IgE by high affinity Fc epsilon receptors in response to allergens. II) through the activation of the anaphylatoxins in the complement C1q, C3a, C4, and C5a molecules, which are responsible for non-IgE-mediated mast cell degranulation. In patients who experience catastrophic cerebral events or renal failure, this complement system activation involving IL-5 and tryptase is far more prevalent than is generally acknowledged. III) by the mas-related G protein-coupled receptor X (MRGPRX2), a low affinity receptor that may activate mast cells by way of non-Fce receptors. IV) Neuropeptides such as substance P (SP), neurotensin (NT), and corticotropin-releasing hormone (CRH) communicate with high-affinity receptors.[21] Histamine, neutral proteases, byproducts of arachidonic acid, platelet activating factor, and a range of cytokines and chemokines that are generated throughout the activation process is some of the inflammatory mediators that cause it. The activation cascade also includes a subgroup of platelets with FCeRI and FCeRII receptors. All of these inflammatory cells take part in a vicious cycle of inflammation and communicate with one another in different ways, such as when mast cells increase T cell activation, T cells mediate mast cell activation and proliferation, mast cells activate macrophages, and T cells control macrophage activity.[20,21] Histamine has also been linked to thrombosis and the activation of platelets. Heart blocks of varied degrees are caused by the mast cells in the heart tissue, which also play a role in allergy, cause tachycardia, change ventricular contractility, and obstruct atrioventricular conduction. Rennin can cause cardiac failure and is also released during allergy episodes.[22–24]

Diagnostic criteria

Although the ECG may be normal or only reflect generic ST-T wave abnormalities, ST elevations in anterior and inferior leads have been the most often seen findings in individuals with KS on electrocardiography. To determine the diagnosis, a thorough laboratory workup is frequently required, including cardiac enzymes and troponins. It is advised to check for alternative causes of coronary syndromes, especially in younger patients: Serologic testing for viral infections are required if myopericarditis has to be considered as a differential diagnosis. Transthoracic echocardiography may be helpful in distinguishing KS from other causes of chest discomfort, such as pericarditis or aortic dissection; the most common results are segmental wall motion abnormalities, which go away a few days or weeks following the acute phase of the disease. Coronary angiography is usually required for differential diagnosis and to evaluate coronary architecture.[25–28]

Treatment

Due to the simultaneous and fast onset of allergy and cardiac symptoms, the induction of shock state, and cardiac arrest, Kounis syndrome treatment may be challenging.[29] Because medications used to treat cardiac manifestations might increase allergies and medications used to treat allergic symptoms can worsen cardiac dysfunction, Kounis syndrome should be treated with great caution.[30] While keeping in mind that some drugs may have an impact on coronary blood flow, the primary goal of therapy should be to prevent life-threatening anaphylaxis. When anaphylaxis is treated, airway edema and obstruction are reduced, interstitial tissue fluid losses are reduced, and tissue oxygenation and perfusion are improved.[31] The first step in treating Kounis syndrome is to stop the allergic reaction, then use medical/interventional procedures to stabilize the coronary vasculature.[32] Cardio logical assessment and treatment of ACS and emergency treatment of acute allergic responses are the two primary therapy facets.[33]

Oxygen administration: Patients with acute coronary syndromes who have respiratory distress, an arterial saturation below 93%, or other high-risk characteristics for hypoxemia should get additional oxygen.[32] The provision of 100% oxygen and any necessary breathing assistance are crucial for individuals who are experiencing anaphylactic shock. As a result, we advise oxygen supplementation as a first line of treatment for Kounis syndrome patients.[34]

Management of type I Kounis syndrome

According to the severity of the clinical picture, Kounis syndrome type 1 (allergic vasospastic angina caused by endothelial dysfunction) should be treated.[35] The main form of therapy for anaphylaxis, a potentially fatal systemic allergic response, is intramuscular adrenaline. The usage of fluids is considerably more crucial in cases of distributive cardiovascular shock and anaphylaxis. Hypovolemia and hemoconcentration are brought on by the intravascular volume shifting into the interstitial space by up to 40%. The important and essential therapy for anaphylaxis is volume expansion. Normal saline, lactated Ringer's solution, or colloid solutions should be given to an adult at an initial dosage of 25–50 ml/kg. During the insult, patients with Kounis syndrome may experience left ventricular dysfunction. Pulmonary edema and respiratory failure may result from a sudden increase in left ventricular end-diastolic pressure and excessive fluid replenishment.[36–38] Systemic or intracoronary nitrates as well as calcium channel blockers, such as diltiazem and verapamil, were frequently used and seem to be acceptable treatment options for such patients[39] in the Type I variant of KS, for which coronary vasospasm is the initial pathophysiologic mechanism for coronary hypoperfusion.[39]

Intravenous corticosteroids: Corticosteroids up-regulate the death receptor CD95 and its ligand CD95L, induce the secretion of annexins (lipocortins), which modulate inflammatory cell activation, adhesion molecule expression, transmigratory, and phagocytic functions, and inhibit the release of arachidonic acid from cell membrane and prevent eicosanoid biosynthesis (via phospholipase A2 inhibition).[40,41] A biphasic anaphylactic response is simultaneously prevented by corticosteroids' positive effects on vascular hyperreactivity and inflammation.[42] Strong immunosuppressive and anti-inflammatory drugs, corticosteroids play a significant part in the management of

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allergic responses. Kounis syndrome is treated with intravenous corticosteroids, such as hydrocortisone, at a dosage of 5 mg/kg/day. Although additional research is required, it is likely safe and effective to use corticosteroids to treat Kounis syndrome.[43]

H1 and H2 antihistamines: Administering intravenous antihistamines slowly can prevent hypotension and additional coronary hypoperfusion. In hospitalized patients, famotidine, an H2 histamine receptor blocker used to treat Kounis syndrome, is associated with a decreased incidence of intubation or death.[44,45] We advised patients with Kounis syndrome to use H1 antagonists once their hemodynamics were stable.[46] In individuals with acute coronary syndromes who use antiplatelet and antithrombotic medications, H2 blockers may prevent gastrointestinal bleeding. In individuals with Kounis syndrome, both H1 and H2 antihistaminic medications must be used. Kounis syndrome is treated with H1 and H2 antihistamines, such as diphenhydramine at a dose of 1-2 mg/kg and ranitidine at a dose of 1 mg/kg, respectively.[47]

Vasodilators: The vasospasm can be stopped by vasodilators such nitrates and calcium channel blockers. Hypersensitivity-related vasospasm can be treated with vasodilators such calcium channel blockers and nitrates. Giving individuals with Kounis syndrome intravenous or sublingual nitroglycerin seems reasonable and safe if their blood pressure is normal.[48]

Nitroglycerin: Myocardial preload is decreased, peripheral and coronary arteries are dilated by nitroglycerin, and myocardial oxygen supply is improved. Patients with acute coronary syndromes who continue to have ischemia discomfort should take three doses of sublingual nitroglycerin (0.4 mg) every five minutes.[49] In the absence of symptomatic heart failure or right ventricular infarction, nitrates should not be given to acute coronary syndrome patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 bpm), or tachycardia (more than 100 bpm). Therefore, if the blood pressure is good, using intravenous or sublingual nitroglycerin in individuals with Kounis syndrome appears appropriate and safe.[50,51]

Calcium-channel blockers: In the absence of clinically significant left ventricular dysfunction or other contraindications, non-dihydropyridine calcium channel blockers (such as verapamil or diltiazem) should be used as the primary treatment to patients with acute coronary syndromes.[52] Although calcium channel blockers may be the initial anti-ischemic medicine of choice in patients with Kounis syndrome, they are not the first line of treatment for acute coronary syndromes.[53]

Management of type II Kounis syndrome

According to the most current recommendations,[54] an acute coronary syndrome protocol should be followed in cases of Kounis syndrome type 2 (allergic myocardial infarction). With corticosteroids, antihistamines, vasodilators like nitroglycerin, or Ca2+ Channel blockers, the allergic reaction can be treated as in type 1 syndrome, with an emphasis on the medications' potentially hazardous cardiac side effects. The treatment of a probable acute anaphylaxis with adrenaline and a -adrenergic agonist may not be beneficial if the patient takes -blockers on a long-term basis for cardiac issues; glucagon may be a worthwhile option.[55,56]

Beta-blockers: Beta-blockers prevent catecholamines from acting on beta-receptors found on cell membranes. For individuals who do not have one or more of the following, oral beta-blocker medication should be started during the first 24 hours: 1) Heart failure symptoms, 2) Low-output state data, 3) Increased Cardiogenic Shock Risk, or 4) Other Relative Contraindications to Beta Blockade (PR interval greater than 0.24 s, second or third degree heart block, uncontrolled asthma, or reactive airway disease). Because alpha-adrenergic receptors do not resist their activity, beta-blockers can exacerbate coronary spasm. In this situation, glucagon infusion (1–5 mg, intravenously over 5 min, then infusion 5–15 g/min) may be administered.Patients who do not react to epinephrine can also be treated with the powerful alpha agonist methocamine.[57–61]

Morphine: Morphine has strong analgesic and calming properties. If ischemic chest pain is not managed by nitroglycerin and further medication is needed to treat the underlying ischemia, patients should be given morphine sulfate intravenously if there are no contraindications to its usage.[58,62] Opiates including morphine, codeine, and meperidine should only be used under the strictest supervision since they have the potential to cause severe mast cell degranulation and exacerbate allergic reactions. It is better to use fentanyl and its derivatives, which only slightly activate mast cells. Because paracetamol (acetaminophen) may produce severe hypotension owing to a drop in cardiac output, it is not advised to take it, especially not intravenously.[63,64]

Management of type III Kounis syndrome

Acute coronary syndrome protocol should be followed, and either a new stent should be deployed or an allergic stent thrombosis with occluding thrombus or stent restenosis with type 3 Kounis syndrome should be performed. It should be advised to combine steroid and antihistamine usage with mast cell stabilizers. The allergic reaction should be managed as previously mentioned, with extra caution for any cardiac side effects of the medications that might exacerbate the clinical situation.[65–68]

Mast cell stabilizers: Mast cell activation is the initial mechanism causing the Kounis syndrome. These drugs, such sodium cromoglycate and ketotifen, may be able to reduce thrombotic events and lessen allergic reactions.[69] Aspirating an intrastent thrombus right away and histologically evaluating it with eosinophil (hematoxylin and eosin) and mast cell staining are recent recommendations for acute myocardial infarction (Giemsa). For allergy symptoms and indications that occur following stent installation, antihistamines, corticosteroids, and mast cell stabilizers are required. When symptoms are persistent, desensitization procedures and patch and/or prick skin tests should be done to identify the source.[69–71]

Conclusion

Acute cardiac events brought on by anaphylactic or anaphylactoid reactions characterize the unusual clinical condition known as Kounis syndrome. Prior allergy history, hypertension, smoking, diabetes, and hyperlipidemia are risk factors for KS. There are three main varieties of Kounis syndrome, including type I coronary spasm, type II acute myocardial infarction caused by coronary erosive lesions, and type III stent thrombosis brought on by localized allergic inflammation. Mast cells that interact with macrophages and T lymphocytes are the earliest inflammatory cells involved in the development of Kounis syndrome. Myocardial preload is decreased, peripheral and coronary arteries are dilated by nitroglycerin, and myocardial oxygen supply is hastened.

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Data sources

Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, Scielo, and Cochrane database are only a few of the sources that were looked up. Risk factors, pathogenesis, and treatment of Kounis syndrome were among the search phrases used.

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