

Kounis Syndrome Following Beta-Lactam Antibiotic Use: Review of Literature

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Abstract: *Background:* Patients with anaphylaxis can have acute coronary syndromes secondary to allergic mediator effects on coronary vessels. Information about these cases is restricted to isolated case reports.

Methods: To review this topic we identified all cases in the PubMed database in English with searches using beta-lactams\adverse effects and several coronary disease MeSH terms.

Results: We analyzed 17 cases with a median age of 60 (range 13 to 72). Seventy-six percent of the patients were men. The beta-lactam antibiotic was administered by oral, IV, and intramuscular routes. Thirteen patients had cutaneous reactions, seven had respiratory symptoms, two had GI symptoms, 11 had chest pain, and 12 had hypotension. All reactions except one developed within 30 minutes. Ten patients had an elevated troponin levels. ECG revealed ST segment elevation in all patients except one. Cardiac catheterization was normal in 10 patients and abnormal in five patients. Allergy testing identified four patients with positive skin tests to antibiotics, four with increased IgE levels, three with increased histamine and tryptase levels, and one with a positive leukocyte transformation test. Treatment included drugs for anaphylaxis and acute coronary syndrome. All patients survived.

Conclusions: Patients with anaphylaxis can present with acute coronary syndrome secondary to either vasospasm or acute plaque rupture and thrombus formation. The typical patient is a man with cutaneous, respiratory and cardiac symptoms and with ST segment elevation in inferior leads. The pathogenesis involves histamine and other mast cell mediators. Management should include therapy for anaphylaxis and vasospasmolytics. The use of epinephrine requires caution.

Keywords: Allergy, angina pectoris, epinephrine, beta-lactams, Kounis.

INTRODUCTION

In 1950, Pfister reported a 49-year-old man who developed anteroapical myocardial infarction and urticaria after four days of treatment with 300,000 units/day penicillin in oil [1]. He described this case as a prolonged sensitivity reaction to penicillin complicated by acute myocardial infarction. The patient was treated with dicumarol, papaverine, morphine, and Benadryl. In 1991, Kounis described the syndrome of "allergic angina". He defined this syndrome as "the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult." [2] Following this publication, cardiologists have reported other cases, including some with acute myocardial infarction. Kounis syndrome now refers to the clinical spectrum of angina pectoris to acute myocardial infarction after an allergic reaction to food, drugs, or insect stings [3]. Based on the pathophysiological mechanism(s) and presence of coronary artery disease, this syndrome is classified into two variants. The type I variant refers to the cases with normal coronary arteries and without atherosclerotic risk factors. The mechanism involves coronary vasospasm triggered by the allergic mediators, such as histamine,

thromboxane, and leukotrienes. The type II variant refers to the cases that occur in patients with silent coronary artery disease and atheromatous vessels. In these patients, allergic mediators induce plaque erosion and rupture which precipitate an acute coronary syndrome.

Tigen, *et al.* [4] reported a 40-year-old woman who developed severe allergic reaction after ingesting one amoxicillin pill. She was initially treated with intravenous steroids and antihistamines. Ninety minutes after the amoxicillin ingestion, she developed retrosternal chest pain. ECG revealed ST segment elevation in the inferior leads. An emergent coronary angiogram and intravascular ultrasound (IVUS) study revealed a noncritically obstructing atherosclerotic plaque with superimposed thrombus in the right coronary artery. She was treated with intravenous glycoprotein IIb/IIIa inhibitor (tirofiban) and anti-ischemic treatment and recovered. Follow-up coronary angiogram and IVUS study showed complete resolution of the thrombus but a persistent plaque. This case stimulated our review of the literature on acute coronary syndromes secondary to beta-lactam antibiotics. These presentations are uncommon but likely underdiagnosed, and clinicians should know about this potentially lethal complication associated with these frequently prescribed antibiotics.

METHODS

We searched the PubMed data base with the MeSH terms beta-lactams\adverse effects combined with the MeSH terms

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coronary artery disease, or coronary vasospasm, or acute coronary syndrome, or coronary thrombosis, or myocardial ischemia. We repeated these searches with the Mesh terms cephalosporins/adverse effects and with penicillins/adverse effects. We also used the text word Kounis syndrome, and we used the related articles algorithm in PubMed. Finally, we reviewed the reference list in each identified article carefully. We used only articles in which the authors' primary conclusion was that the patient had an acute coronary event related to beta-lactam allergy and which were in English.

CLINICAL CASES

We identified 17 case reports (Table 1) [4-19]. The mean age was 53 (median 60) with a range of 13 to 72. Seventy-six percent of the patients were men. The drugs involved included penicillin, ampicillin, amoxicillin, cefuroxime, cefoperazone, cefoxitin. Medications were delivered by an oral route in eight patients, an IV route in eight patients, and an intramuscular route in one patient. Thirteen patients had cutaneous reactions, seven patients had respiratory symptoms or signs, and two patients had GI symptoms. Cardiac symptoms included chest pain in 11 patients and decreased blood pressure in 12 patients. The time between medication delivery and symptoms ranged from immediate to 150 minutes. All reactions except one developed within 30 minutes. Ten patients had increased troponin levels and five patients had normal troponin levels. ECG revealed ST segment elevation in all patients except one (exact result unclear). Cardiac catheterization results were normal in ten patients and abnormal in five patients. Immunologic/allergic testing in-

cluded four positive skin tests, four increased IgE levels, three increased histamine levels, three increased tryptase levels, and one positive leukocyte transformation test. Treatment included epinephrine (n=4), corticosteroids (n=13), H1 blockers (n=12), H2 blockers (n=6), morphine (n=2), nitroglycerine (n=8), aspirin (n=3), and β -blockers (n=1) (Table 2). Twelve patients had Kounis type 1 syndrome, and five patients had Kounis type 2 syndrome. All patients survived.

CASE ANALYSIS

Our review of these case reports indicates that the typical patient with the Kounis syndrome is a middle-aged man who develops symptoms within 30 minutes of administration of a drug (in this series beta-lactam antibiotics). Symptoms usually include rash and dyspnea associated with chest pain and hypotension. These patients have ST elevation in the inferior leads. Most of the patients have either normal or noncritical coronary artery disease demonstrated by coronary angiography. Therefore, coronary vasospasm produces the cardiac symptoms in most of these cases. These patients respond to drugs used for anaphylaxis but, in addition, often receive treatment for acute coronary syndrome, given the potential uncertainty about diagnoses at presentation. Although the number of cases published is limited, this syndrome seems to have less mortality and a better short term prognosis than the usual acute coronary syndrome, and this may reflect differences in pathogenesis or the success of treatment focused on the allergic reaction and associated vasospasm. Aspirin use was limited among these cases either because of underreport-

Table 1.

Age/Sex [Ref.]	Drug Route	Allergic Symptoms	Cardiac Symptoms	Time (Minutes)	TROP	ECG	Cath	Other	Diagnosis
72 ♂ [5]	Amp-Sulb PO	R	Hypo	15	↑		Multivessel dis	↑ IGE	K2
63 ♀ [6]	Amp-Sulb IV	?	CP Hypo	10	ND	↑ ST inf	Minimal dis	-	K1
40 ♀ [4]	Amox PO	C	CP	20	↑	↑ ST inf	50% RCA / thrombus	-	K2
32 ♂ [7]	Amox PO	C R GI	CP Hypo	150	↑	↑ ST inf	Normal	+ skin test	K1
56 ♂ [8]	Amox PO	C R	CP	30	↑	↑ ST inf & V3-6	ND	+ skin test ↑ IGE	K1
70 ♀ [9]	Cefuroxime IV	C	CP Hypo	1	NI	? NI	Normal	↑ IGE H T	K1
72 ♂ [10]	Cefoperazone IV	C	Hypo	Immediate	↑	↑ ST inf	Normal	Lymph trans	K1
55 ♀ [11]	Pen IM	C	Hypo	3	NI	↑ ST inf & V6	Normal	-	K1
56 ♂ [12]	Pen IV	C R GI	CP Hypo	2	NI	↑ ST inf	Normal	↑ IGE H T Eo	K1
61 ♂ [12]	Pen IV	C	CP	1	↑	↑ ST inf	ND	↑ IGE H T Eo	K2
21 ♂ [13]	Pen IV	R	Hypo	Immediate	↑	↑ ST 1,aVL, V2-3	Normal	-	K1
13 ♂ [14]	Amox/C PO	C	CP	30	↑	↑ ST inf & lat	Normal	↑ T	K1
69 ♂ [15]	Amox IV	--	CP Hypo	Few	NI	↑ ST inf	Normal	Repeated episode	K1
70 ♂ [16]	Amox PO	C R	Collapsed	Few	↑	↑ ST 2	LAD	+ skin test	K2
61 ♂ [17]	Amox/C PO	C	CP	10	↑	↑ ST V1-3	CAD	Prior episode	K2
64 ♂ [18]	Cefoxitin IV	C R	Hypo	10	NI	↑ ST inf & ↓ ST V2-6	Normal	-	K1
43 ♂ [19]	Amox/C PO	C	CP Hypo	Immediate	NI	↑ ST inf	Normal	+ skin test	K1

Amp - ampicillin, Sulb - sulbactam, Amox - amoxicillin, Pen - penicillin, C - clavulanate, C - cutaneous, R - respiratory, CP - chest pain, Hypo - hypotension, Inf - inferior leads (II, III, AVF), ND - not done, H - histamine, T - tryptase, K1 - Kounis type 1, K2 - Kounis type 2, CAD - Coronary artery disease, TROP - Troponin, LAD - Left anterior descending coronary artery, Eo - Eosinophil, IV - Intravenous, PO - Per oral, IM - Intramuscular.

Table 2. Treatment

Patient #, [Ref.]	Epinephrine	H ₁ blocker	H ₂ blocker	Steroids	Nitro	Heparin	ASA	Other
72 ♂, [5]						+	+	β-agonist Atrovent
63 ♀, [6]					+			Norepinephrine
40 ♀, [4]		+		+				Tirofiban
32 ♂, [7]	+	+	+	+	+	+	+	β-agonist, norepinephrine, thrombolytic
56 ♂, [8]		+		+	+			
70 ♀, [9]		+	+	+				Morphine
72 ♂, [10]	+			+	+			Ephedrine, dopamine
55 ♀, [11]	+	+	+	+				Dopamine
56 ♂, [12]				+	+			Morphine, Atropine
60 ♂, [12]		+	+	+	+			Morphine, Beta-blocker
21 ♂, [13]		+	+	+		+		Ketotifen
13 ♂, [14]		+		+				
69 ♂, [15]					+			Steroids + nitro (2 nd episode)
70 ♂, [16]		+	+	+	+		+	
61 ♂, [17]		+						Dopamine
64 ♂, [18]	+	+		+				
43 ♂, [19]		+		+				Angina medication

ing or because of an effort to avoid the addition of another potentially allergic drug. Only four patients received epinephrine.

Patients with Kounis syndrome usually present with inferior wall myocardial ischemia/infarction and often have angiographically normal coronary arteries. The right coronary artery is the most frequent site of coronary vasospasm for uncertain reasons. These patients may have endothelial dysfunction, smooth muscle calcium hypersensitivity, increased autonomic tone, increased oxidative stress, genetic susceptibility, or a combination of these factors which disproportionately affect the right coronary artery.

PATHOGENESIS

Tissue mast cells are the primary cells involved in allergic reactions. Mastocytes originate from progenitor cells in the bone marrow, circulate as undifferentiated mononuclear cells in the peripheral circulation, migrate into the tissues, and subsequently mature under the influence of locally derived growth factors and cytokines. Cardiac mast cells have been demonstrated in the coronary artery intimal layer and atherosclerotic plaques. Inside the plaques they are commonly localized in critical areas such as the shoulder region and modulate the process of atherosclerosis from its onset to plaque rupture [20]. Kovanen, *et al.* have demonstrated that the density of mast cells in the culprit atheroma of patients who died from acute myocardial infarction was 200 times higher than the density in normal coronary vessels from the same patients [21]. Cardiac mast cells can respond to the allergic stimuli like the mast cells in the lung and skin. During the allergic reaction these mast cells become activated and release endogenous mediators, including histamine, leukotrienes, thromboxane, platelet activation factor (PAF),

tryptase, chymase, and renin. These biogenic products affect different receptors on the vessel wall and precipitate acute coronary syndromes. Histamine increases the movement of calcium ions into the myocardial cells and accelerates phase 4 spontaneous depolarization of the ventricular action potential. Histamine stimulates the sinus node and increases the atrioventricular nodal and ventricular automaticity which makes the heart prone to arrhythmias. Histamine increases cardiac contractility and heart rate and causes coronary vasospasm through H₁ and H₂ receptors. These effects distort the O₂ balance in myocardial cells. Activation of H₁ receptors on endothelial cells stimulates the release of prostaglandins, interleukin 6, and interleukin 8 into the circulation which causes inflammation. Histamine also induces tissue factor expression and contributes to thrombus formation in acute coronary syndromes [22]. In addition to direct coronary vasoconstricting and thrombus generating effects, histamine also potentiates the platelet aggregating response to adrenaline. These direct and indirect effects of histamine have a central role in the pathogenesis of the acute coronary syndrome secondary to allergic reactions. Antihistamines inhibit histamine-induced tissue factor expression and have potential beneficial effects in acute coronary syndromes. Similarly, blockage of H₃ histaminic receptors has been demonstrated to improve left ventricular systolic function in an animal model of anaphylactic shock [23]. Leukotrienes and thromboxane also cause coronary vasoconstriction. Cardiac mast cells release significant quantities of chymase and renin in comparison to lung and skin mast cells. Chymase and renin activate the angiotensin system and convert angiotensin I to angiotensin II, a potent vasoconstrictor. Angiotensin II promotes the local secretion of noradrenaline which is arrhythmogenic and induces myocardial ischemia. Tryptase and chymase activate matrix metalloproteinases and contrib-

ute to the plaque erosion or rupture [24]. Platelet activation and intracoronary thrombosis are triggered by histamine, PAF, and thromboxane. PAF decreases coronary blood flow and myocardial contractility and has direct arrhythmogenic effects [25]. This change in blood flow reflects both direct PAF effects and indirect PAF effects mediated by its release of leukotrienes and thromboxane. PAF causes instability and rupture of atherosclerotic plaques by inducing local platelet aggregation and releasing lytic enzymes from macrophages. It also induces peripheral vasodilation and may increase hypotension. Plasma PAF levels correlate with the severity of anaphylaxis. Therefore, both histamine and PAF cause coronary vasoconstriction and peripheral vasodilation, and these two effects reduce myocardial perfusion.

BETA-LACTAM ANTIBIOTICS AND ANAPHYLAXIS

Beta lactam antibiotics are relatively safe drugs but do cause allergic reactions. These reactions vary in type (Type 1 to Type 5) and in severity (mild rash to anaphylaxis). Allergic reactions occur in 1-4% of patients, and anaphylaxis may occur in up to 0.015% of patients [26]. The induction of allergic reactions, including anaphylaxis, occurs after "sensitization" of an individual to specific allergen (antibiotics in these patients) and can occur at any age. Drug exposure typically activates the antigen presenting cells on body surfaces in contact with the outside environment, and these cells present the allergen(s) to the T helper cells. T helper cells respond to this event with either a TH1 type response (e.g., contact dermatitis) or a TH2 type response (e.g., IgE mediated anaphylaxis). The TH2 type response activates specific B cells which, in turn, transform into plasma cells. These plasma cells synthesize and release allergen-specific IgE which binds to (sensitizes) mast cells and basophils. Mast cells are preferentially located on mucosal and submucosal surfaces but also reside in perivascular locations. They respond rapidly to repeat exposure to specific allergens with a coordinated allergic reaction leading to acute mediator release and sustained inflammatory response [26].

WORK-UP

Acute onset chest pain accompanied by allergic symptoms should raise suspicion for the possibility of Kounis syndrome. In addition to the routine work-up of patients with acute coronary syndromes (ECG, cardiac enzymes and troponin), serum histamine, tryptase, specific IgE antibody, complement proteins (C4 and C1 inhibitor levels), and eosinophil levels can help identify this syndrome. Serum tryptase levels document mast cell activation; however, a negative tryptase test does not exclude this possibility. Elevated serum histamine and tryptase level strongly support the possibility of an ongoing allergic reaction, but these molecules have very short half lives (less than 10 minutes for histamine and 90 minutes for tryptase) that make them relatively inconvenient for the routine use. Eventually these patients will need coronary angiograms with or without intravascular ultrasound studies to assess the coronary anatomy, possibly relieve vasospasm directly with intracoronary agents, and perform angioplasty when needed. During the follow-up, patients may need further allergy work-up including skin prick tests.

MANAGEMENT

Acute coronary syndromes secondary to allergic reactions are associated with significant morbidity and mortality in hypersensitive individuals. The systemic allergic response caused by inflammatory mediators should be controlled early in the management of these patients.

1. All patients should be questioned carefully regarding their allergy profile before their treatment with a potentially allergic drug such as a beta-lactam antibiotic.
2. Kounis syndrome should be considered in young, healthy patients with no atherosclerotic risk factors when they develop acute coronary syndrome (especially inferior myocardial infarction) after administration of beta-lactam antibiotics. These patients need treatment with steroids, antihistamines, fluid resuscitation, and possibly epinephrine in addition to oxygen and antithrombotics before transfer to the cardiac catheterization laboratory.
3. The treatment should both dilate coronary vessels and suppress the allergic reaction. Vasospasmolytic agents, including nitrates and calcium channel blockers, should be considered first-line therapy in young and previously healthy individuals since vasospasm is the primary mechanism. Corticosteroids have also been used successfully in the treatment of refractory vasospastic angina, particularly when the patients have an allergic diathesis [27]. Acute coronary syndrome protocol should be followed in patients with a Type II variant.
4. Whether or not to use epinephrine is a challenging decision in acute coronary syndromes secondary to an allergic reaction. Epinephrine is a life-saving medication in anaphylaxis; however, it has a narrow therapeutic window. In concurrent cases of allergic reaction and acute coronary syndrome, its risks may outweigh the benefits. First, most epinephrine preparations contain sulfite as a preservative and antioxidant which itself may trigger anaphylaxis in sensitive individuals. Second, it can aggravate the ischemia, prolong QTc interval, and induce coronary vasospasm and arrhythmias. Elderly patients, especially with a history of hypertension and coronary artery disease, are prone to these side effects. Therefore, epinephrine should be used even more cautiously in this group. Third, the use of intravenous epinephrine is still controversial in severe allergic reactions. It should be considered in patients with severe hypotension or cardiac arrest who do not respond to aggressive fluid resuscitation. The intravenous route of epinephrine administration can cause uncontrolled elevation in blood pressure and precipitate intracranial bleeding. Intramuscular use of epinephrine is the safer and preferred route of administration unless the patient has severe anaphylaxis. Finally, some patients may have received beta-blockers in the initial management of the acute coronary syndrome, and the usual dose of epinephrine may be ineffective. It may also promote more vasospasm secondary to unopposed alpha adrenergic effect in patients who have received beta-blocking agents. Glucagon may be considered for pa-

tients who are already on beta-blockers or received them during the management of the acute coronary syndrome. Methoxamine, a potent alpha agonist, can also be considered in patients who do not respond to epinephrine.

Consensus opinion on epinephrine use during anaphylaxis favors epinephrine administration as soon as anaphylactic symptoms occur [28, 29]. According to the current guidelines, there is no absolute contraindication to epinephrine use in anaphylaxis. The recommended dose and route is 0.2-0.5 mg of aqueous epinephrine (1:1000) administered intramuscularly in the thigh every 5-15 minutes. In patients with cardiac arrest intravenous epinephrine (1:10,000 to 1:100,000) can be considered. Obviously, these recommendations stem from all types of anaphylaxis cases in which most of the patients did not have a concurrent acute coronary syndrome. More case studies are needed to establish the use of epinephrine in patients with Kounis syndrome.

5. Opiate medications, like morphine, codeine and meperidine, should be used cautiously in this group of patients since they can induce massive mast cell degranulation and aggravate the allergic reaction. Fentanyl and its derivatives show only a slight activation of mast cells and should be the drugs of choice when narcotic analgesia is necessary.
6. Although their efficacy and potency is questionable, mast cell membrane stabilizers (e.g. sodium cromoglycate, ketotifen) may be considered in patients who develop acute coronary syndromes after drug reaction and have been used in some cases.

KEY POINTS

Beta-lactam antibiotics may cause allergic reactions and initiate an acute coronary syndrome in hypersensitive individuals. Clinicians should be aware of this syndrome and tailor the management accordingly. Antihistamines and steroids are necessary in addition to the anti-ischemic therapy. Epinephrine therapy should be considered in hypotensive patients secondary to anaphylaxis. Coronary vasospasm should be treated with nitrates and/or calcium channel blockers. Careful reviewing of the allergy history or skin testing in complex cases before prescribing these agents will reduce the incidence of Kounis syndrome secondary to beta-lactam antibiotics.

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