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Case Report

Cardiac arrest in type II Kounis syndrome after oral intake of amoxicilline

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Abstract: Background: Kounis syndrome (KS) is defined as the occurrence of an acute coronary syndrome related to allergic or hypersensitivity reaction. KS is currently classified into three variants, based on coronary arteries status. This syndrome is often neglected or misdiagnosed in clinical practice. Methods and results: We described a type II KS case. This acute coronary syndrome (ACS) began with cardiac arrest (an uncommon clinical expression for KS) immediately after oral intake of amoxicilline. Coronary angiography revealed coronary arteries stenoses which were considered unsuitable for revascularization. Optimization of medical therapies was the goal of the management for this patient. Follow-up visits revealed normal echocardiographic findings and no malignant arrhythmias at ECG Holter monitoring. Conclusions: KS can be a rare case for ACS, sometimes occurring with sudden cardiac arrest. Physicians should pay attention to the history of the patients in order to identify the correct cause of ACSs.

Keywords: Allergy, amoxicilline, anaphylaxis, cardiac arrest, coronary spasm, Kounis syndrome

Introduction

Kounis syndrome (KS) is an acute coronary syndrome (ACS) induced by an allergic or hypersensitivity and anaphylactic or anaphylactoid reaction to outer substances [1, 2]. The annual incidence of KS is about 4-19 cases/100.000 individuals, the prevalence reaching 1.1% in those admitted for allergy conditions [2]. Three variants can be identified: Type I: ACS with normal coronary arteries and no predisposing factors for coronary artery disease (CAD); Type II: ACS in pre-existing atheromatous CAD; Type III: ACS due to thrombosis into drug-eluting coronary stents and/or coronary stent restenosis [2].

The pathogenesis is still a matter of debate. Allergic stimuli can cause spastic contraction of the smooth muscle cells into the walls of coronary arteries due to the action of histamine, leukotrienes, and serotonin released from mast cells [2]. Histological reports outlined the infiltration of mast cells, eosinophils, and lymphocytes in coronaries [3].

Different triggers can cause allergic reaction: food (fish, fruits, vegetables, etc.), drugs (antibiotics, nonsteroidal anti-inflammatory drugs [NSAIDs], anticancer drugs, etc.), environmental exposure (insects bites) [2, 4]. The consequence is the occurrence of angina and/or ACS [2, 5].

Treatment actually focuses on both symptoms of allergic reactions and ACS [2]. The use of epinephrine is debated as it improves anaphylaxis but increases oxygen consumption [2].

In particular, type II variant considers emergency coronary angiography examination and corticosteroids/antihistamines administration as first-line therapy [2].

We described the case of a type II KS occurring with cardiac arrest after oral intake of amoxicillin.

Case report

A 62-year-old former smoker man, suffering from hypertension, dyslipidaemia, diabetes mellitus was admitted to the emergency department (ED) due to general asthenia. He had previous history of NSAIDs and penicillin-allergy (five months before he experienced face erythema after preoperative intake of amoxicillin for dentistry intervention). Soon after ED access, sudden cardiac arrest occurred: the patient underwent advanced life support treatment (2 gr of adrenaline were immediately administered due to the occurrence of asystolia), with prompt recovery of cardiac rhythm despite the persistence of coma, gasping, muco-cutaneous cyanosis, and miosis. He was apyretic and tachycardic (heart rate 105 bpm), with blood pressure 130/80 mmHg. Arterial blood gas analysis (ABG) revealed hypercapnic hypoxia (pO_2: 57 mmHg, pCO_2: 58 mmHg) and metabolic acidosis (pH: 7.1), therefore orotracheal intubation for mechanical ventilation was performed and bicarbonate were administered. Biochemical analysis revealed increase in white blood cells count (17500/μL, neutrophils 15000/μL), and mild augmentation of high-sensivity troponin levels (64 pg/ml). Cranial and thoracic CT did not show any neurological emergency, except signs of pulmonary emphysema and sinusopathy. ECG showed ST segment elevation in the inferior leads, with specular anterior ST segment depression (**Figure 1A**, **1B**).

Transthoracic echocardiography (TTE) showed hypertensive heart disease (interventricular septum diastolic diameter: 12.5 mm, left ventricle end-diastolic diameter: 49 mm, aortic root diameter: 39 mm, E/A ratio <1), normal contractility, and preserved left ventricle ejection fraction (55%). Emergency coronary angiography revealed long, subcritic (70%) stenosis at medium tract of the left anterior descending artery (LAD); long, subcritic (60%) stenosis at proximal-medium tract of the first diagonal artery; short, critic (95%) stenosis at distal tract of the posterior descending artery (PDA) (**Figure 1C**, **1D**). No revascularization was performed and medical therapy was the final destination therapy for this patient.

The patient was transferred to the Department of Anaesthesia and Intensive Care Medicine, and weaned off invasive ventilation the day after the index event. A full medical interview was then performed. The patient reported that he had assumed 500 mg amoxicillin for dental care prophylaxis immediately before the symptoms onset. Clinical course was good and the patient was discharged about one week after the admission. At 30-day follow-up, the patient showed normal LVEF; the 24 h ECG Holter outlined sinus rhythm, heart rate between 56 and 112 bpm, rare supraventricular extra systoles, and rare ventricular, monomorphic, non-repetitive, ventricular extra systoles; no conduction abnormalities were detected, as well as no transient, ischemic alterations could be observed. Similar results were evident at three months follow-up.

Discussion

KS is often a neglected diagnosis in the context of ACS [2]. This is the first case of type II KS ACS related to amoxicilline intake occurring with cardiac arrest [6]. Literature provides case reports about the KS as the main pathogenetic background of ACS in patients who ingested antibiotics [4] and amoxicilline in particular [7-19] (see **Table 1**). The anaphylactic reaction to the drugs is able to promote the activation of mast cells and the release of their granules [2]. The exocytosis of histamine, cytokines, chemokine, etc. is able to promote vascular inflammation, coronary spasms, and plaque ruptures [2]. When such events occur in the backgroung of an already damaged coronary vascular endothelium due to atherosclerotic plaques, a type II KS ACS is developed [2]. Canpolat et al. [8] reported the case of an appropriate implantable defibrillator (ICD) shock due to ventricular fibrillation (VF) in a patient suffering with non-ischemic dilated cardiomyopathy. Indeed, a possible interaction with the polymers and the constituents of the ICD might predispose the patient to the development of an inflammatory cardiac foundation able to promote the occurrence of VF in the context of amoxicillin-induced KS [9].

Duarte et al. [10] reported the case of a 73 year-old patient who experienced cardiorespiratory arrest and EGC alterations related to ACS after the ingestion of amoxicillin/clavulanic acid. Indeed, this was considered as a type I KS as no coronary obstruction or atheroscle-

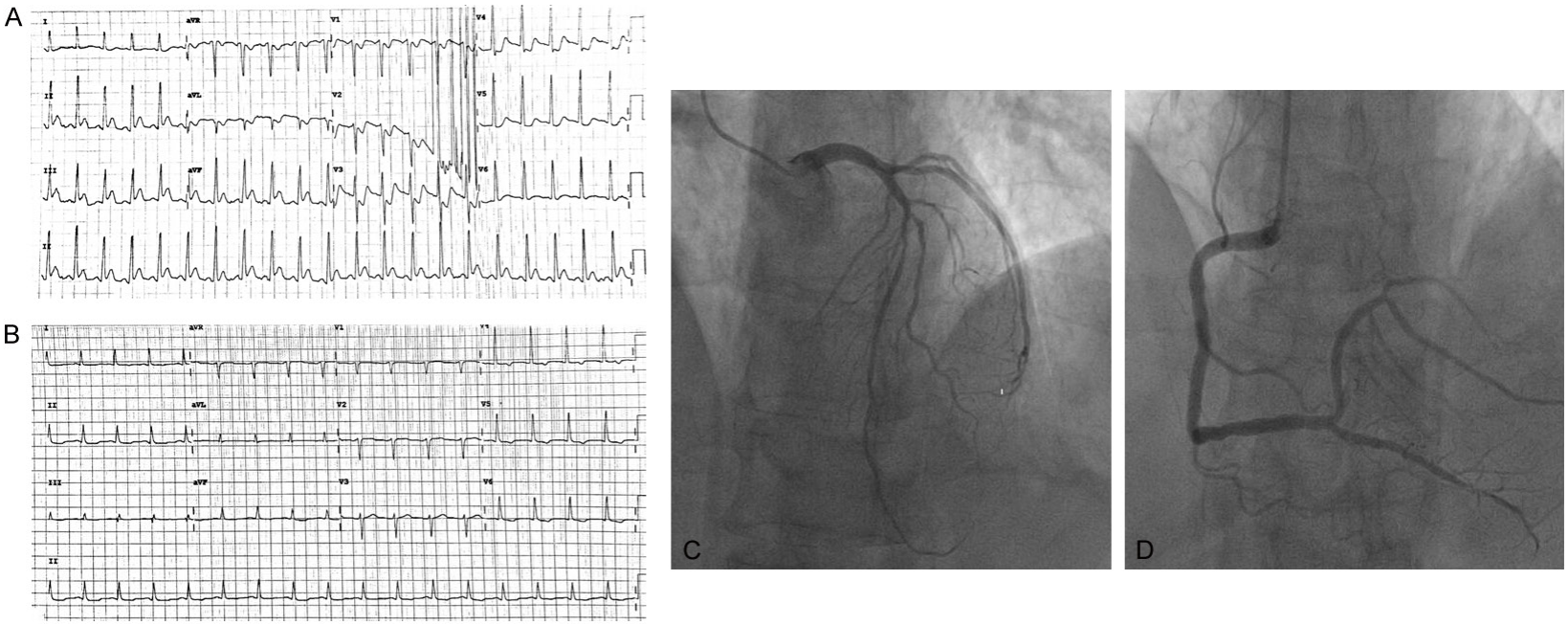

Figure 1. Electrocardiogram. A: ST segment elevation in the inferior leads in acute phase. B: ECG at 24 hours after the index event. Coronary artery status during coronary angiography. C: Left artery coronary. D: Right coronary artery.

Table 1. Literature overview about Kounis syndrome occurrence after amoxicillin intake

Source	Age	Gender	Drug	KS type	Symptoms	Cardiac Arrest
Pradhan et al. 2018 [7]	22-year-old	M	Amoxicillin	I	ST elevation and elevated cardiac biomarkers	No
Canpolat et al. 2018 [8]	54-year-old	M	Amoxicillin/clavulanic acid	I	implantable cardioverter defibrillator (ICD) shock on ICD	Yes
Duarte et al. 2020 [10]	54-year-old	M	Amoxicillin/clavulanic acid	I	Cardiorespiratory arrest and ACS occurrence	Yes
Shimi et al. 2016 [11]	56-year-old	F	Amoxicillin/clavulanic acid	I	ST modification and ACS symptoms	No
Bezgin et al. 2013 [12]	29-year-old	M	Amoxicillin/clavulanic acid	I	ST modification and ACS symptoms	No
Biteker et al. 2009 [16]	13-year-old	M	Amoxicillin/clavulanic acid	I	ST modification and ACS symptoms	No
Mazarakis et al. 2012 [20]	64-year-old	M	Amoxicillin	II	ST modification and ACS symptoms	No
Omri et al. [21]	60-year-old	M	Amoxicillin	II	ST modification and ACS symptoms	No
Caglar et al. 2011 [15]	31-year-old	M	Amoxicillin/clavulanic acid	II	ST modification and ACS symptoms	No
Viana-Tejedor et al. 2011 [14]	64-year old	M	Amoxicillin	II	ST modification and ACS symptoms	No
Tigen et al. 2007 [17]	40-year-old	F	Amoxicillin	II	ST modification and ACS symptoms	No
Tavil et al. 2008 [18]	61-year-old	M	Amoxicillin/clavulanic acid	II	ST modification and ACS symptoms	No
Del Furia et al. 2007 [19]	70-year-old	F	Amoxicillin/clavulanic acid	II	ST modification and ACS symptoms	No
Salouage et al. 2016 [6]	58-year-old	F	Amoxicillin/clavulanic acid	III	anaphylactic shock and chest pain	No
Venturini et al. 2011 [13]	48-year-old	M	Amoxicillin	III	ST modification and ACS symptoms	No

rotic plaque were detected at coronary angiography, as well as no coronary revascularization was previously performed [10].

Salouage et al. outlined the occurrence of type III KS after the intake of amoxicillin [6]. Indeed, the fatal expression of the syndrome in this context can be mediated by the interplay between coronary stent components and the allergic reaction to amoxicillin. Mazarakis et al. [20] reported a type II KS ACS involving the left main coronary artery in a 64 years old patient after oral administration of 1 g of amoxicillin. No aborted sudden cardiac death occurred, but urgent revascularization procedure and early use of hydrocortisone and antihistamine were able to solve the clinical situation [20]. A similar case was described by Omri et al. [21]: a 60-year-old man developed a type II KS ACS with no cardiac arrest after amoxicillin intake, thus undergoing cath-lab for revascularization procedure on proximal circumflex artery.

Our case pointed out the occurrence of ACS after the ingestion of amoxicillin. As the coronary angiography outlined a compromised vascular coronary bed, a type II KS was diagnosed, although occurring directly via sudden cardiac arrest. Although cardiac arrest can occur in the context of coronary artery spasm with or without the presence of atherosclerotic plaques [22], no other cases of abrupt cardiac arrest have been described in literature in the context of type II KS.

Conclusions

The KS can rarely occur with cardiac arrest. Firstly, this case highlighted KS as a possible cause of ACS, not to be forgotten; secondly, allergic condition can trigger ACS which can express with cardiac arrest; finally, the administration of adrenaline in such a context might be beneficial in order to counteract anaphylactic/anaphylactoid reactions both peripherally and/or centrally. Clinical history of the patient should be closely evaluated.

Disclosure of conflict of interest

None.

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