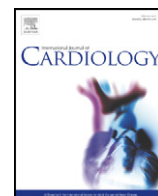




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Letter to the Editor

Kounis Syndrome induced by intravenous administration of piperacillin/tazobactam: A case report

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Kounis Syndrome (KS) is the concurrence of an acute coronary event with conditions associated with a massive mast-cell degranulation, usually during anaphylactic or anaphylactoid reaction [1]. KS seems to be promoted by inflammatory mediators, as histamine, chemokines and leukotrienes released by cardiac mast cells [2], able to induce a coronary vasospasm [1,2]. KS was firstly described in 1991 by Kounis and Zavras as allergic angina progressing to “allergic myocardial infarction” [3]. KS can be induced by Hymenoptera stings, food allergy and of course various drugs as well as contrast media, intravenous anaesthetics, NSAIDs and, of course, antibiotics [1]. Betalactams are the commonest cause of drug induced KS and amoxicillin is the most frequently culprit betalactam molecule [4]. We described a KS in a 62-year old man following tazobactam/ piperacillin infusion.

An obese non atopic 62 years old man was admitted to the 4th Pneumologic Division of Hospital A. Galateo (Lecce) for an acute pneumonia coming from the First Aid Center of the Civil Hospital Vito Fazzi. The patient claimed cough, malaise and slight chest constriction with no fever or dyspnea. The chest X-ray confirmed presence of a pneumonic process on the basal right lung. Laboratory tests showed a slight neutrophilic leucocytosis (WBC: 12.200/mm³) with a mild hyperglycemia (1.24). Pulse oxymetry was satisfactory (97%) and the electrocardiography (ECG) showed a normal frequency with sinus rhythm. Blood pressure was good (80/130 mm Hg). Thoracic objec-

tive examination showed thin basal rattles on the right base with moderate pain in the same area. He denied to have any drug allergy. He reported to have been previously admitted twice in the General Civil Hospital Vito Fazzi, firstly in March 2002 at the Cardiac Surgery Unit for a partial rupture of a misdiagnosed thoracic aorta aneurysm and then in November 2005 at the Thoracic Surgery Department for a spontaneous pneumothorax.

A brachial venous catheter line was positioned and theophylline, methylprednisolone succinate and furosemide were administered intravenously, followed by tazobactam/piperacillin 4.5 grams.

Within few minutes he had a diffuse erythematous rash on his trunk, neck, face and arms bilaterally with intense itching. Patient showed malaise, shortness of breath and he quickly became hypotensive and tachycardic (approximately 140 bpm). Blood pressure collapsed to 70/40 mm Hg and he was hypoxic to 78/79% oxygen saturation. Antibiotic administration was promptly stopped, while tremors and dyspnea appeared. Furthermore, he was sweaty and reported intense chest and abdominal pains. One gram of hydrocortisone succinate was injected intravenously, followed by chlorpheniramine maleate diluted in 100 ml of saline solution with high flow oxygen rate through a Venturi mask.

Patient still reported a strong thoracic pain and an urgent 12 leads ECG was performed, revealing tachycardia, isolated extrasystoles and a ST depression in leads V4, V5, V6 (Fig. 1). It suggested an acute ischemic heart injury. Cardiologist was alerted and another bolus of hydrocortisone succinate was injected intravenously. Taking advantage of a slight increase of blood pressure (60/90), cardiologist arranged for contemporary administration of hydrocortisone both to a very slow infusion of nitrates. As soon as chest pain faded, infusion of the latter drug was stopped immediately. No epinephrine was administered.

Patient improved and pulse-oxymetry demonstrated increased oxygen saturation of 92% as blood pressure augmented too (70/100). A slow administration of injectable corticosteroid associated to a proton pump inhibitor was performed all night long to prevent biphasic anaphylaxis.

Cardiac enzymes were measured after the acute episode and six hours later. No mast cell tryptase was performed.

Furthermore total IgE and specific IgE to Penicillin G, Penicillin V, amoxicillin and Ampicillin (Phadia ImmunoCAP, Uppsala, Sweden) were investigated on the next morning after the anaphylactic episode and three days later. The results of cardiac enzymes, total and specific IgE dosage are showed in Tables 1 and 2.

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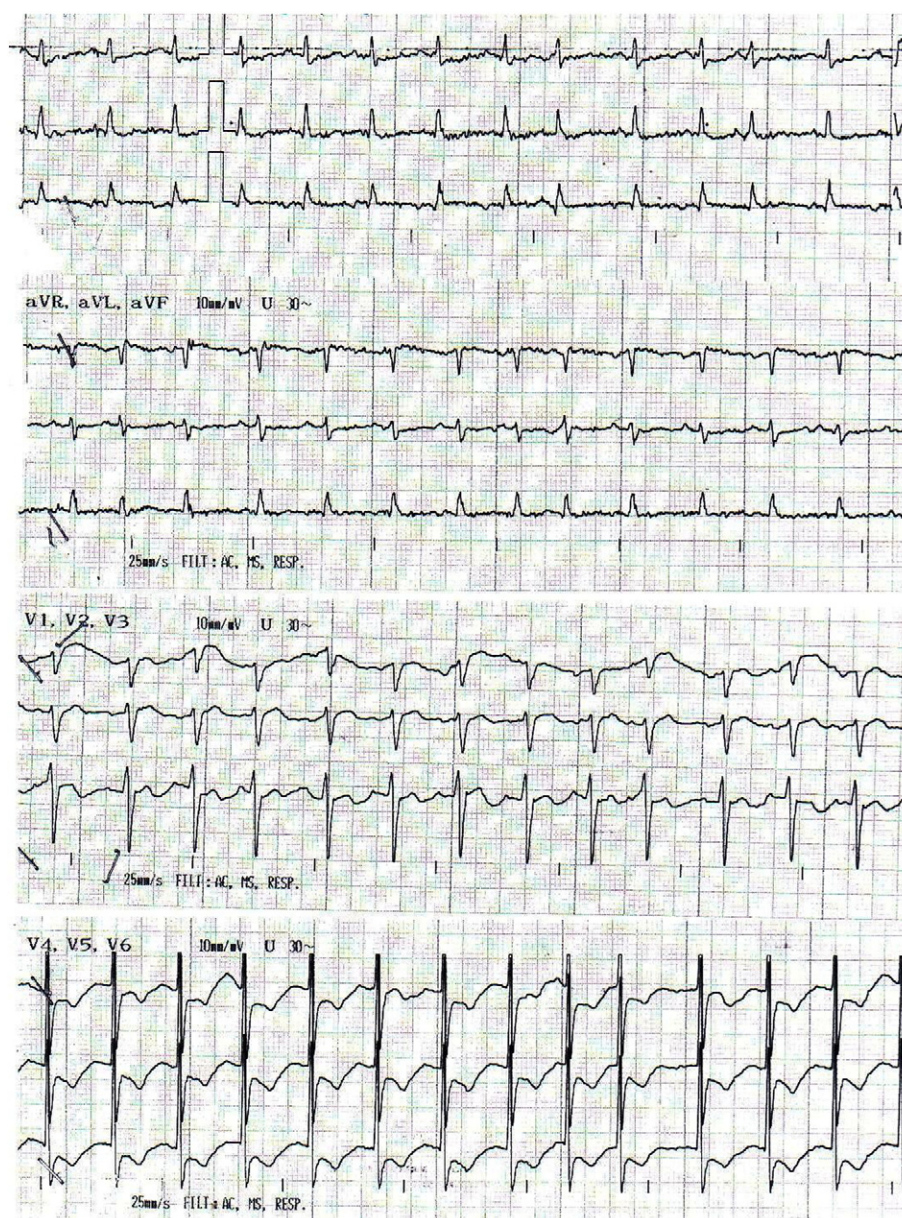


Fig. 1. ECG showing tachycardia, occasional extrasystoles and ischemic ST depression in V4, V5, V6.

Moreover our patient showed a boosted IgE response three days later. He refused any coronary angiography.

Detailed medical history showed that the patient had undergone previous treatment with Sulbactam/Ampicillin 3 grams tris in die for 20 days during the first hospitalization in 2002, while a course of tazobactam/piperacillin 4.5 grams bis in die had been used for 12 days during the second hospital admission in 2005.

Patient was dyslipidemic. He was treated with levofloxacin 500 mg and he was discharged 10 days later. Chest–X-ray, cardiac enzymes had been returned to normal, but total IgE showed a high value yet.

Because of risk of another episode KS, no skin allergic tests were carried out. One year later, in an allergic follow up, patient still showed increased value of total IgE (179 UI/ml) and a mild hypercholesterolemia.

The Kounis Syndrome or allergic angina is a myocardial ischemia associated to an immediate-type hypersensitivity reaction, usually an anaphylactic or an anaphylactoid reaction, but exceptionally it may be associated to an urticaria even [5]. Such cardiac ischemia considerably complicates the course and treatment of the anaphylaxis itself, which already represents a life-threatening medical emergency.

Two variants of KS have been described [6]: the 1st variant occurs in patients with apparently normal coronaries who do not report risk factors predisposing towards coronary ischemia. The acute allergic reaction determines a coronary vasospasm that may induce, but not

Table 1
Evaluation of cardiac enzymes at different times.

Cardiac enzymes	Time intervals		
	0 hours	6 hours later	9 days later
Lactic dehydrogenase (normal range 266–500 U/l)	599 U/l	712 U/l	462 U/l
Creatine phosphokinase (normal value <180 U/l)	145 U/l	404 U/l	51 U/l
Creatine phosphokinase MB fraction (normal value <5 ng/ml)	4 ng/ml	7.63 ng/ml	2.2 ng/ml
Myoglobin (normal value <72 ng/ml)	211 ng/ml	414 ng/ml	68 ng/ml
Troponin (normal value <0.10 ng/ml)	<0.10 ng/ml	<0.10 ng/ml	<0.10 ng/ml

Table 2
Immunological evaluation at different times.

	8 hours later	3 days later	9 days later	45 days later
Total IgE ^a	54 IU/ml	556 IU/ml	519 IU/ml	503 IU/ml
Specific IgE ^b to:				
Penicillin G	0.04 kUA/l	0.05 kUA/l		
Penicillin V	0.07 kUA/l	0.06 kUA/l		
Ampicillin	0.23 ^b kUA/l	0.25 ^b kUA/l		
Amoxicillin	0.03 kUA/l	0.04 kUA/l		

^a Normal value <100 IU/ml.

^b Values for specific IgE >0.1 kUA/l indicate sensitization.

necessarily, ECG alterations and increase cardiac enzymes and/or troponins potentially evolving toward an acute heart attack. This 1st variant may represent a demonstration of a misdiagnosed endothelial dysfunction as in microvascular angina. The 2nd variant includes patients with pre-existing atheromatous lesions on coronary vessels. The vasospasm induced by acute allergic reaction may predispose the erosion or the break-up of the atheromatous plate, evolving more frequently toward an acute myocardial infarction [6].

Recently a 3rd variant has been suggested including patients with coronary artery stents thrombosis in whom eosinophils and mast cells were isolated in thrombus [7]. Patients with previously positioned metal or medical coronary stents seems to be likely to develop a KS during a hypersensitivity reaction [8], probably because metal foreign bodies or medical stents in coronary vessels may stimulate local mast cells proliferation [8].

Interestingly, in 2002, our patient had undergone to an urgent heart surgery where aortic stumps have been tightened with Teflon strips, but no coronary stents had been introduced in heart vessels.

The KS can appear in elderly [9] as well as in paediatric age [10], although predictive risk factors have not been identified.

Actually in literature more than 30 cases of KS betalactams-induced have been reported [4] and amoxicillin is the most frequently involved molecule, followed by Ampicillin, Penicillin G and various cephalosporins, but no case of KS due to piperacillin/tazobactam infusion have been never previously reported.

Piperacillin is a highly effective ureidopenicillin which rarely induces immediate-type allergic reactions. Piperacillin is seldom associated to tazobactam, a betalactamase inhibitor. The combined antibiotic is active against many Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*.

We found a few reports regarding immediate-type allergic reaction due to piperacillin [11–13] and piperacillin/tazobactam [14], but, in all of them, IgE-mediated patho-mechanism has been elucidated by skin tests only, because the RAST prototype to piperacillin was unsatisfactory [11,12], although recently specific IgE to piperacillin have been evidenced *in vitro* by the use of a piperacillin–human–serum–albumin–conjugate in a 24-year old nurse professionally exposed to that antibiotic [15].

Because our laboratory did not have the commercial assay for mast cell tryptase dosage, we choose to evidence indirectly the IgE-mediated mechanism by monitoring the IgE boosted response in the days following the anaphylactic episode, as previously suggested by Blanca et al. [16].

Moreover, our patient showed meaningful serum levels of specific IgE to Ampicillin.

Such antibiotic had been used in 2002 during patient hospitalization in the Cardiac Surgery Unit. Interestingly he showed significant presence of specific IgE to Ampicillin (see Table 1), still detectable 8 years far from its use, thus suggesting he was predisposed to develop IgE sensitization towards betalactam antibiotics.

Neither Penicillin G nor amoxicillin specific IgE levels were detected or increased in the third day control as total IgE did, by suggesting patient had specific IgE to piperacillin or tazobactam. Romano et al. already demonstrated the selective sensitization to piperacillin [11], because IgE antibodies may be preferably direct towards antibiotic side chain reactive group, which is very bulky in piperacillin molecule [11]. In

that report, indeed patient was able to tolerate Ampicillin and penicillin V in single blind placebo controlled oral challenge tests [11], but we choose not to carry out any skin tests even in our patient because of the possibility to trigger another KS, as previously reported [17].

Finally, although epinephrine is considered the foremost drug in anaphylaxis treatment, its use in KS is quite controversial [18], because epinephrine may aggravate the present ischemia, prolong QT trait, induce arrhythmias and above all, may facilitate atheromatous plaque rupture for the sudden blood pressure increase [18]. For that reason, patient was treated with intravenous high dosages of glucocorticoids alternated with nitrates. According to some Japanese authors, high dosages of intravenous corticosteroids may be more effective and safer to alleviate coronary allergic vasospasm in KS [19].

The KS potentially represents a lethal and underestimated clinical emergency whose treatment requires an urgent intensive-type therapy with a high cardiac expertise. Nevertheless, KS seems to be increasingly reported so it is opportune that allergist/immunologist knows every anaphylactic reaction may be further complicated by an allergic coronary vasospasm, potentially progressing toward an allergic myocardial infarction, even in young patients.

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The authors of this manuscript have certified that they comply with the principles of ethical publishing in the International Journal of Cardiology [20].

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