

Beware of the dog: a case report on cardiac involvement in drug allergy

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To the Editor. Severe anaphylaxis often involves the cardiovascular system, with symptoms due both to vasodilatation and increased vascular permeability and to the direct cardiotoxicity of mast cell mediators.^{1–4} Nevertheless acute myocardial infarction (MI) complicating drug-induced anaphylaxis is uncommon.⁵

The high numbers of mast cells in heart tissue, mainly located around coronary vessels and in proximity to the pacemaker region of the sinoatrial node, may explain the heart involvement in anaphylaxis.^{1,3} Consequently, coronary spasm may easily occur.^{6–8}

In addition, mast cells are likely to affect coagulation and fibrinolysis, and mediators from interstitial and perivascular mast cells may promote platelet aggregation and thrombus formation.^{3,9}

Therefore, acute ST elevation MI (STEMI) is a potential complication of anaphylactic reactions.^{10–12}

Here, we present the case of a 58-year-old man who developed acute MI following amoxicillin-induced anaphylaxis on two different occasions. Three months after the second occasion, a curious thing happened. ...

Methods

A 58-year-old man was admitted to the emergency care unit because of urticaria and hypotension, warmth, flushing and thoracic pain. Ten minutes earlier he had ingested amoxicillin/clavulanic acid (1 g) and paracetamol/chlorphenamine (300/2 mg) (Zeranol) for a sore throat. On admission, he was conscious, his blood pressure (BP) was 80/60 mmHg, pulse rate 80 bpm and oxygen saturation 77%. His history revealed essential systemic hypertension treated with candesartan/hydrochlorothiazide (16/12.5 mg once daily) (Blopresid),

type II diabetes mellitus treated with rosiglitazone/metformin (2/1000 mg twice daily) (Avandamet), obesity (weight = 130 kg), hypercholesterolemia and smoking habit (about 60 cigarettes/day).

Immediately methylprednisolone (125 mg) and ranitidine (50 mg) were administered intravenously (i.v.); morphine (20 mg), acetylsalicylic acid (500 mg) and heparin (1 ml) were also administered and the patient was connected to a cardiac monitor: a 12-lead ECG showed ST segment elevation in leads II, III, aVF and V4 to V6 (STEMI). The peak level of serum creatine phosphokinase (CPK) was 3134 U/l (normal = 34–190 U/l), whereas the CPK-MB fraction was 417 U/l (normal = 1–24 U/l).

Results

Coronary angiography showed severe right coronary atherosclerosis (one-vessel disease) with thrombotic occlusion of the distal segment [thrombolysis in myocardial infarction (TIMI) 0]. Percutaneous transluminal coronary angioplasty (PTCA) was immediately performed and a bare metal stent was placed on the distal segment of the right coronary artery, with complete revascularization (TIMI 3).

This intervention was complicated by recurrent ventricular fibrillation (treated with repeated electric shock, with restoration of the sinus rhythm) and by respiratory failure (following aspiration) that required tracheostomy.

Although he was admitted to the ICU, he manifested acute renal failure (peak level of creatine = 2.25 mg/dl, normal = 0.7–1.2 mg/dl) and neurological failure with complete resolution in the following days (normal electroencephalography).

An echocardiographic study performed 1 day after admission showed mild left ventricular hypertrophy, ejection fraction of 55% and akinesia of the lower septum and lower wall. The patient was discharged 1 month after admission.

Two months later the patient was again admitted to the emergency care unit for urticaria and hypotension that appeared 15 min after self-administration of amoxicillin (1 g) for dental pain, followed by tachycardia, warmth, asthenia and epigastric pain.

The patient was conscious, BP 90/60 mmHg, pulse rate 120 bpm, oxygen saturation 90%. A 12-lead ECG showed STEMI at the same location. The peak level of serum CPK was 231 U/l (normal = 34–190 U/l), whereas the CPK-MB fraction was 49 ng/ml (normal = 0.50–4.00 ng/ml). Moreover, an increase of troponin-I was observed 5 h later (7.14 ng/ml, normal value 0–0.10 ng/ml). He was treated with methylprednisolone (125 mg i.v.), acetylsalicylic acid and ephinephrine.

Coronary angiography showed complete obstruction of the distal segment of the right coronary artery (TIMI 0), without thrombosis. PTCA was immediately performed, but the simple insertion of the guide wire into the artery resulted in complete revascularization (TIMI 3). An echocardiographic study performed 1 day after admission was fully comparable to the previous one. After 1 week the patient had completely recovered and was discharged.

Because of a suspected hypersensitivity to amoxycillin, he was at last referred to the Allergy Unit of Spedali Civili of Brescia. Previously, he never experienced adverse drug reactions with betalactam antibiotics. He reported only that his sister had adverse reactions to penicillins.

Serum specific immunoglobulin E (IgE) to penicilloyl V, penicilloyl G, amoxycillin, ampicillin and ceftriaxone were not detectable (CAP System, Phadia, Uppsala, Sweden).

Skin tests were performed according to the position paper of the European Network for Drug Allergy–European Academy of Allergy and Clinical Immunology Interest Group on Drug Hypersensitivity,¹³ using penicilloyl polylysine (PPL) and minor determinant mixture (MDM) (Diater Laboratories, Madrid, Spain), ampicillin, amoxycillin, ceftriaxone. A strongly positive test to ampicillin and amoxycillin (4+ reaction on a scale of 1–4) appeared after a few minutes.

Three months after the second myocardial infarction a curious thing happened. The patient was licked on face by his dog and quickly he manifested acute urticaria and periorbital angioedema. The patient went to the emergency room where he was given methylprednisolone (125 mg i.v.), ranitidine (50 mg) and chlorphenamine (10 mg), with rapid resolution of symptoms; after 2 hours he was discharged. Investigation revealed that amoxycillin was administered to the dog half an hour before by a veterinary surgeon.

Comment

The prevalence of adverse reaction to betalactams in the general population ranges from 0.7 to 10%.¹⁴ Among these, type I reactions are often associated with systemic manifestations that range from urticaria/angioedema to hypotension and anaphylaxis.¹⁵ However, clinically similar non-IgE-mediated reactions may occur.¹⁶ A

personal history of atopy does not represent an increased risk for a type I penicillin reaction;¹⁷ however, atopic patients may have more severe anaphylactic reactions.¹⁷

Acute coronary syndromes have been described as potential complications of anaphylactic reactions. The hypothesis suggested for the pathogenesis of MI refers to so-called 'cardiac anaphylaxis', including the functional and metabolic changes in the heart caused by the release of histamine and vasoactive mediators by cardiac mast cells.^{18,19}

The mechanism inducing acute myocardial ischemia is not yet completely understood. Coronary vasospasm is one of the mechanisms proposed, superimposed on a fixed coronary lesion in up to 60% of cases, but may also occur in normal coronary arteries.^{11,20} H1 receptors, expressed on vascular smooth cells, mediate coronary vasoconstriction and increase vascular permeability such that massive histamine release from mast cells during anaphylactic reactions may trigger coronary spasm.^{21,22} Coronary spasm can be caused by other mast cell-derived vasoactive mediators, such as prostaglandin D₂ and leukotrienes.²³

Moreover, mast cells may also induce plaque activation in patients with underlying coronary atherosclerosis,²³ so mast cells are an important component of inflammatory infiltrate of eroded/ruptured plaques.²⁴

Another possible mechanism is prolonged hypotension, especially in patients with critical coronary stenosis; in fact, a sudden reduction of coronary flow in the territory of the stenotic artery might produce MI.

Last but not least, antianaphylactic drugs (i.e. epinephrine) used to treat hypotension might also worsen a coronary spasm induced by mast cell mediators.²⁵ Often it is not clear which mechanism predominates.

We reported the case of a 58-year-old man who experienced two anaphylactic reactions following amoxycillin intake, complicated by STEMI. In the first, an acute thrombotic occlusion at the site of coronary stenosis (perhaps facilitated by coronary spasm induced by mast cell mediators and hypotension) seems to have been the main pathogenic mechanism. In the second, acute MI was probably caused by the sudden drop in coronary perfusion due to systemic hypotension.

The pathogenic role of the amoxycillin was suspected only after the second acute MI, mainly because of the rapid, complete resolution of the coronary obstruction with the simple insertion of the guide wire into the obstructed artery.

Skin-prick tests confirmed an IgE-mediated sensitization to amoxycillin. In this patient additive risk factors (hypercholesterolemia, obesity, type II diabetes mellitus, smoking habits) are likely to have played a role, but the recurrence of the events with the third administration

enforces the causative role of amoxycillin. The third event, albeit limited, confirmed the high individual susceptibility to amoxycillin.

It is, therefore, to be kept in mind that MI may complicate anaphylactic reactions and that patients who undergo anaphylactic reaction should be carefully monitored.

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