



Letter

Ventricular fibrillation after oral administration of amoxicillin and clavulanic acid

Systemic anaphylaxis represents the most significant and potentially catastrophic manifestation of immediate hypersensitivity. This syndrome can affect virtually any organ in the body, although reactions that involve the pulmonary, circulatory, cutaneous, neurologic, and gastrointestinal systems are the most common. Reactions range widely in severity from mild pruritus and urticaria to shock and even death.¹

The most common triggers of anaphylactic reaction are food, venom from stinging insects, and medications. Antibiotics, especially β -lactam antibiotics, are often involved.² Only a few reports of electrocardiographic (ECG) changes after anaphylaxis have been reported. The ECG changes included ST-segment depression or elevation, T-wave changes, arrhythmias, or conduction disturbance.³ We describe a patient with severe anaphylaxis after oral administration of amoxicillin and clavulanic acid in which the patient developed ventricular fibrillation (VF).

A 52-year-old woman with the cardiovascular risk factors of smoking, hypertension, and hyperlipidemia was referred for a dental operation. Her medications included a statin, low-dose β -blocker, and angiotensin-converting enzyme inhibitor. Per routine protocol, antibiotics for dental infection prevention were recommended. She took a single dose of 875 mg of amoxicillin–clavulanic acid (Augmentin; GSK Brentford, Middlesex, United Kingdom). Ten minutes after taking the medication, she felt general weakness, confusion, and itching. She had diarrhea followed by nausea and vomiting. A rash developed.

Her husband called emergency services. An intensive care ambulance arrived several minutes later, a dose of 0.3 mL of adrenaline was injected subcutaneously, and she was connected to an ECG monitor. Sinus tachycardia was initially diagnosed. After a few minutes, when en route to the hospital, she lost consciousness and VF was observed via the monitor. Immediately, a 200-J DC shock was administered, and the patient regained consciousness and returned to normal sinus rhythm.

The patient was admitted to the intensive coronary care unit alert in stable condition. Physical examination findings were unremarkable. The ECG on admission did not reveal any abnormalities. Blood analysis revealed a high white blood cell count of 18,440/ μ L. All other laboratory values, including potassium and other electrolytes, were within the reference range. Echocardiography revealed normal left ventricular systolic function and normal right ventricular systolic function. There was no evidence of cardiomyopathy, left ventricular segmental wall motion abnormalities, or any valvular heart disease.

Coronary angiography found mild atherosclerosis without significant narrowing. Cardiac magnetic resonance imaging revealed no evidence for myocarditis or any abnormalities. The heart chambers were within normal volumes and had normal function. Multichannel 24-hour Holter ECG monitoring revealed a normal sinus rhythm with few atrial premature beats and a minimal number of ventricular premature beats with normal QTc interval throughout the recording.

During her stay, she was continuously monitored and no arrhythmias were detected. The conclusion was that VF was due to a severe reaction to the amoxicillin–clavulanic acid.

Few reports of cardiac arrhythmia related to anaphylaxis have been published, especially cardiac arrhythmia related to cardiovascular collapse. These changes were variable and included ST-segment elevation and depression, nodal rhythm, prolonged QT interval, and atrial fibrillation.^{3,4} However, there are only 2 reports of VF associated with an anaphylactic reaction.^{5,6} All of the patients experienced VF within a month of amoxicillin–clavulanic acid exposure, both related to insect sting bites. Similar to our report, the diagnosis was reached after obtaining normal results on cardiovascular studies, and a primary cardiac cause of the VF was excluded.

Seventy-eight of 20,276 people (0.38%) with adverse reactions to amoxicillin–clavulanic acid were reported to have VF after taking amoxicillin according to the public service website www.ehealthme.com, which summarizes Food and Drug Administration reports. However, these patients took other medications that may interact and cause VF, and there are no data about association with an anaphylactic reaction.

The VF described in our patient may be explained by the presence of cardiac mast cells adjacent to nerves.⁷ After degranulation by IgE cross-linking in immediate hypersensitivity reactions, mast cells release 2 cell-dependent effectors that can modulate norepinephrine release by targeting sympathetic nerves, renin, and histamine. Renin initiates the activation of a local renin-angiotensin system, which culminates in the formation of angiotensin II.⁸

Angiotensin II is arrhythmogenic and binds to AT₁-receptors, which are also expressed in sympathetic nerves, whereas histamine activates H₃-receptors on sympathetic and sensory nerve endings. The H₃-receptor is cardioprotective by attenuating release of norepinephrine. An imbalance between these 2 pathways affects the release of norepinephrine from cardiac sympathetic nerve during myocardial ischemia and can result in arrhythmias and sudden cardiac death.⁸

Another possible explanation of this reaction is the occurrence of cardiac anaphylaxis after activation of the anaphylaxis toxin complement factors C3a and C5a and release of histamine after food or drug stimulation. This mechanism has been implicated in peanut-induced anaphylaxis in mice, although the significance of this in human anaphylaxis has not been demonstrated. A genetic variation in complement activation (complotype) in determining the severity of allergic reactions to peanut was demonstrated in animal studies. However, a study in humans did not demonstrate this genetic association in patients with peanut allergy.⁹

Kounis syndrome is another entity associated with acute coronary syndrome after ingestion of a drug or food accompanied by symptoms of anaphylaxis.⁴ This is a group of symptoms that manifests as unstable vasospastic or nonvasospastic angina and even as acute myocardial infarction. It is triggered by the release of inflammatory mediators after an allergic, hypersensitivity,

Disclosures: The author have no conflicts of interest.

anaphylactic, or anaphylactoid insult. Although coronary artery disease is usually found, there was not coronary artery disease in this case; thus, this syndrome seems unlikely.

In conclusion, we assume that our patient experienced an anaphylactic reaction with hemodynamic collapse. We exclude the diagnosis of mast cell activation syndrome because the patient met all the clinical definition criteria of anaphylaxis (an acute onset of an illness with involvement of the skin, respiratory, and cardiovascular systems). A diagnosis of mast cell activation syndrome should be considered only if those episodes do not meet the criteria for anaphylaxis.¹⁰ Unfortunately, tryptase levels were not tested. To the best of our knowledge, this is the first report of VF after amoxicillin–clavulanic acid anaphylaxis.

Eduardo Shahar, MD^{*,‡}

Ariel Roguin, MD, PhD^{†,‡}

^{*}Department of Immunology

[†]Department of Cardiology

Rambam-Health Care Campus
Haifa, Israel

[‡]Rappaport Faculty of Medicine
Technion-Israel Institute of Technology
Haifa, Israel

ed_shahar@rambam.health.gov.il

References

- [1] Boghner BS, Lichtenstein LM. Anaphylaxis. *N Engl J Med*. 1991;324:1785–1790.
- [2] Lieberman PL. Anaphylaxis. In: Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske RF, Simons FER, eds. *Middleton's Allergy: Principles and Practice*. 7th ed. St Louis, MO: Mosby Inc; 2009:1027–1049.
- [3] Petsas AA, Kotler MN. Electrocardiographic changes associated with penicillin anaphylaxis. *Chest*. 1973;64:66–69.
- [4] Lombardi N, Pugi A, Maggini V, Lenti MC, Mugelli A, Cecchi E, Vannacci A. Underdiagnosis and pharmacovigilance: the case of allergic acute coronary syndrome (Kounis syndrome). *Clin Ther*. 2013;35:563–571.
- [5] Wojtowicz M, Biernat C. Case of ventricular fibrillation following a bee sting. *Pol Tyg Lek*. 1976;27:2229–2230.
- [6] Quercia O, Emiliani F, Foschi FG, et al. Ventricular fibrillation after a Hymenoptera sting. *Int J Cardiol*. 2008;127:5–7.
- [7] Morrey C, Brazin J, Seyedi N, et al. Interaction between sensory C-fibers and cardiac mast cells in ischemia/reperfusion: activation of a local renin-angiotensin system culminating in severe arrhythmic dysfunction. *J Pharmacol Exp Ther*. 2010;335:76–84.
- [8] Meredith IT, Broughton A, Jennings GL, et al. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *N Engl J Med*. 1991;325:618–624.
- [9] Menikou S, Patel MP, Rose KL, Botto M, Warner JO, Pickering MC. Relationship between comorbidity and reported severity of systemic allergic reactions to peanut. *J Allergy Clin Immunol*. 2012;129:1398–1401.
- [10] Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391.