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Kounis syndrome caused by anaphylaxis without skin manifestations after cefazolin administration

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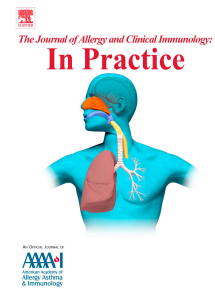
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Clinical Communications

Title

Kounis syndrome caused by anaphylaxis without skin manifestations after cefazolin administration

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Clinical Implications

We report a case of Kounis syndrome, the concurrence of acute coronary syndrome with hypersensitivity reactions, caused by anaphylaxis to cefazolin that was difficult to diagnose because of the absence of skin signs.

Word counts

Clinical Implications: 33 words

Main documents: 1000 words

32 **TO THE EDITOR**

33 Kounis syndrome (KS), also known as allergic angina or allergic acute coronary syndrome, is caused
34 by an allergic reaction^{1,2}. The mechanism of KS involves the release of inflammatory mediators
35 during mast cell activation, which leads to coronary artery vasospasm and atheromatous plaque
36 erosion or rupture^{2,3}. Although infrequently diagnosed, KS results from various causes related to
37 allergy and can occur at any age, thus physicians are likely to eventually encounter this disease. Here,
38 we report a case of KS caused by an anaphylactic reaction to intravenous cefazolin that was difficult
39 to diagnose because of the absence of skin signs.

40 A 92-year-old Japanese woman was admitted to our hospital for bladder cancer surgery.
41 She had no significant medical history, no known allergies, and no significant risk factors for
42 coronary artery disease. In the operation room, 1 g of cefazolin sodium was administered in 100 mL
43 of 0.9% NaCl solution. At 5 min after starting cefazolin sodium administration, lidocaine was
44 injected in and around the lumbar vertebrae for local anesthesia. A Quincke needle was injected into
45 the L4-L5 intervertebral space for subarachnoid block. Shortly afterward, she experienced sudden
46 shortness of breath and nausea. Then, her breathing became stertorous and irregular, oxygen
47 saturation dropped abruptly to 80%, and heart rate decreased to 40 bpm, which was followed by
48 shock and loss of consciousness.

49 These clinical findings initially led to a suspicion of vasovagal response triggered by pain

caused by the lumbar puncture, as there were no skin symptoms. Thus, atropine sulfate, as opposed to adrenaline, was intravenously administered. She did not respond to the infusion of atropine sulfate and her blood pressure remained unrecordable. Hence, she was immediately intubated and kept on assisted ventilation with a mask.

While in a state of shock, an electrocardiogram (ECG) revealed sinus rhythm, ST elevation in leads II, III, and aVF, and reciprocal changes in leads I, aVL, and V3–V5 (Figure 1). Suspecting acute coronary syndrome, diluted nicorandil was immediately administered as a bolus injection. Also, continuous intravenous infusion of noradrenaline was started. Additionally, unfractionated heparin was injected after ruling out stroke on brain computed tomography.

Upon arrival at the cardiac catheterization room, the baseline changes in the ST segment on ECG had improved. Coronary angiography revealed no stenotic lesions causing ST elevation in leads II, III, and aVF. As a result, the probable causes of ST elevation in leads II, III, and aVF included coronary artery spasm. The results of blood analysis showed no characteristic findings and there were no skin symptoms suggestive of anaphylaxis. Thus, the cause of coronary artery spasm was initially thought to be transient low blood pressure caused by a vasovagal response. In such cases, the possibility of KS should be ruled out because of the occurrence of ST segment elevation after antibiotic administration. Therefore, additional examinations were performed after recovery from shock state.

The level of tryptase in a blood sample collected when the patient was in a state of shock was notably elevated at 26.7 $\mu\text{g/L}$ as compared to a normal value of 3.3 $\mu\text{g/L}$ when the patient was stable. Furthermore, the results of a prick testing and intradermal testing showed a strong positive reaction for cefazolin, but negative results for physiological saline, xylocaine, and penicillin (Figure 2).

These results suggested an anaphylactic reaction caused by cefazolin. Therefore, KS was diagnosed based on the concurrence of acute coronary syndrome due to coronary artery spasm.

At the time of bladder cancer surgery, penicillin, as opposed to cefazolin, was selected based on the negative results of the intradermal testing, which resulted in no allergic reaction. After surgery, she was discharged with no complications.

Because there was no specific clinical examination, a diagnosis of KS was established on the basis of signs, symptoms, ECG changes, and angiography. Therefore, the concurrence of acute coronary syndrome with acute allergic reaction should suggest a diagnosis of KS.

First-generation cephalosporin antibiotics, including cefazolin, are currently used for treating infections. There have been a small number of cases of KS due to cefazolin administration⁴. In anaphylaxis, skin symptoms occur in up to 80%–90% of cases⁵. However, in the present case, there were no skin symptoms at all. As a cause of shock, distinguishing anaphylaxis reactions from vasovagal reflexes or cardiogenic shock is difficult in the absence of skin manifestations. Basically,

anaphylaxis is diagnosed by clinical examination. In the present case, acute onset of respiratory symptoms and hypotension occurred after cefazolin administration, which is in agreement with the diagnostic criteria.

Measurement of serum or plasma tryptase can help to determine whether the event is caused by anaphylaxis⁶. Tryptase is more chemically stable than other mast cell materials and has a longer half-life. Moreover, it exists in blood even at several hours after onset and is also easier to assay⁷. Presently, there is no consensus on a treatment for KS. In contrast, epinephrine has been established as the initial medication of choice for anaphylaxis and coronary vasodilators are the first-line drugs for the treatment of coronary artery spasm. On the other hand, previous studies have shown that coronary spasm was induced by stimulation of alpha receptors with epinephrine or norepinephrine⁸. Thus, administration of coronary vasodilators in combination with epinephrine may be considered for KS. Especially, nicorandil, which has high selectivity for the coronary artery and does not reduce blood pressure like other coronary vasodilators, may be effective⁹.

In the present case, the cause of shock was initially thought to be a vasovagal response. Since KS was suspected based on the elevations in the ST segment, anaphylaxis to cefazolin was identified by evaluation of tryptase levels and skin allergy testing, which resulted in a diagnosis of KS.

In conclusion, KS can be encountered at any time, thus ECG examinations of patients with allergic

reactions may be required. Conversely, knowledge of KS will help to confirm a diagnosis of anaphylaxis. Therefore, it is necessary to raise awareness of KS so that appropriate therapeutic interventions and preventative measures can be employed.

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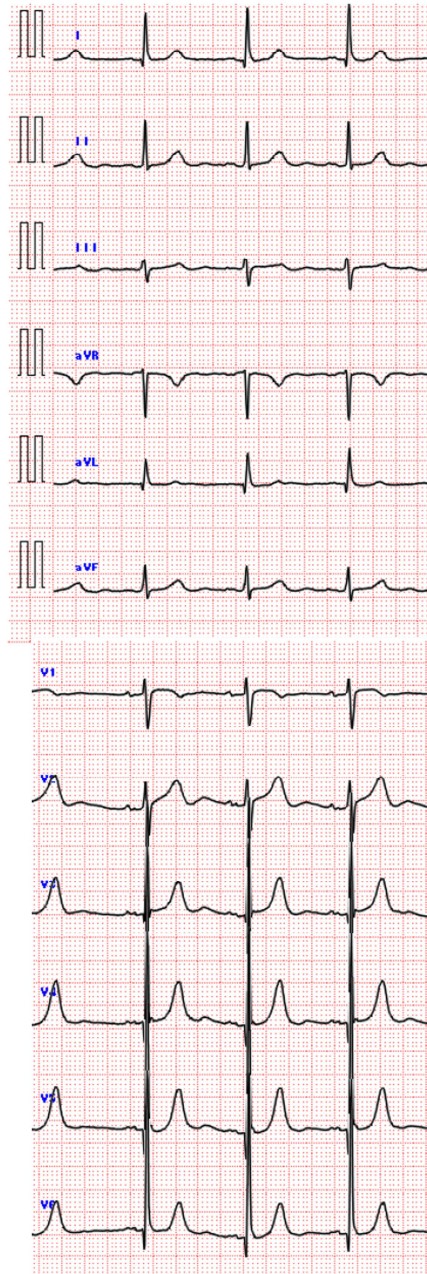
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158 **FIGURE LEGENDS**

159 **FIGURE 1.** The 12-lead electrocardiogram. Preoperative electrocardiogram (A). Electrocardiogram
160 during shock showing ST elevation in leads II, III, and aVF (B).

161

162 **FIGURE 2.** Results of intradermal testing. Intradermal testing showed a strong positive reaction with
163 wheal of 15×17 mm and erythema of 28×31 mm (white arrow heads) for cefazolin, but negative
164 results for physiological saline, xylocaine, and penicillin.

A Preoperative**B** During shock