Case Report

Tazobactam/piperacillin-induced Kounis syndrome, with similar symptoms also triggered by therapeutic administration of methylprednisolone: A case report

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We report a rare case of Kounis syndrome induced by tazobactam/piperacillin (TAZ/PIPC) in a patient who had received multiple prior administrations of the same antibiotic for bacterial pneumonia without event. Notably, the patient also exhibited similar symptoms following administration of methylprednisolone for the treatment of anaphylaxis. The clinical course of this rare case was challenging, yet insightful. A 70-year-old male patient with rheumatoid arthritis and asthma-chronic obstructive disease overlap syndrome (ACOS) developed anaphylactic shock and coronary vasospasm shortly after receiving an injection of TAZ/PIPC. A 12-lead electrocardiogram (ECG) showed marked ST elevation in leads II, III and aVF, and the patient was intubated and initiated on mechanical ventilation. Coronary angiography revealed no obvious stenosis of the coronary arteries. The ST-segment elevation on the ECG also normalized. Based on the findings, the patient was diagnosed as having suffered coronary anaphylaxis (Kounis syndrome type I) and stabilized with epinephrine, norepinephrine, and fluid boluses. Furthermore, the patient also developed anaphylactic shock and ST-segment elevation on the ECG following methylprednisolone administration, which resolved after the drug was switched to betamethasone. This case highlights the importance of rapid diagnosis and balancing treatment for both anaphylaxis and acute coronary syndromes in these patients.

Key words: Kounis syndrome, anaphylaxis, coronary vasospasm, tazobactam/piperacillin, methylprednisolone

I. Introduction

Kounis syndrome is defined as an acute coronary syndrome associated with allergic reactions, that is induced by histamine and other mediators released by mast cells[1)]. The first case of acute coronary syndrome associated with anaphylaxis was reported in 1950 in a patient who developed myocardial infarction after receiving a penicillin injection[2)]. Subsequently, in 1991, Kounis and Zavras described the pathophysiology of this condition and proposed it as a new clinical entity called "histamine-induced angina syndrome"[2)]. It is thought that any substance that can induce an allergic reaction has the potential to cause Kounis syndrome. Among pharmaceutical products, any drug that elicits an allergic reaction, including antibiotics, contrast media, antiplatelet agents, and anticancer drugs, has the potential to trigger histamine-induced angina syndrome, although antibiotics are thought to be the most common cause[1)].

In Japan, an analysis of cases of anaphylaxis caused by pharmaceuticals showed that antibiotics accounted for 12.4% of all cases of anaphylaxis. The most common causative antibiotic agents are β-lactams, with cephems accounting for 67%, penicillins for 14%, and carbapenems for 3% of all cases[3]. In this study, we report a case of coronary anaphylaxis (Kounis syndrome) caused by tazobactam/piperacillin (TAZ/PIPC) in a patient who developed similar symptoms following therapeutic administration of methylprednisolone.

II. Case report

The patient was a 70-year-old man with underlying rheumatoid arthritis and asthma-chronic obstructive disease overlap syndrome (ACOS), who presented to our Internal Medicine Outpatient Clinic with a day's history of fever (38℃), cough, and purulent sputum. He was receiving inhalational fluticasone-formoterol combination therapy for the treatment of ACOS. He gave a history of developing urticaria with the use of diclofenac sodium and tocilizumab. However, the patient had received the same antibiotic, TAZ/PIPC, without event, for the treatment of pneumonia caused by *Pseudomonas aeruginosa* 30 months, 21 months, 12 months, and 1 month previously. His body weight was 72 kg. The peripheral arterial oxygen saturation was 93% (room air). Chest auscultation revealed coarse crackles over the left lower lung regions. Blood tests revealed elevated inflammatory response marker levels, including a peripheral blood white blood cell (WBC) count of 16,800/μL and serum C-reactive protein (CRP) level of 13.82 mg/dL. Chest computed tomography (CT) showed a consolidation in the lower lobe of the left lung. Based on these findings, the patient was diagnosed as having bacterial pneumonia and started on treatment with intravenous TAZ/PIPC administration at 4.5 g/dose. Fifteen minutes after receiving TAZ/PIPC, the patient developed severe nausea, followed by loss of consciousness and was transported to the emergency room. The patient's level of consciousness was assessed on the Glasgow Coma Scale (GCS) as E1V2M1. At first, we thought that the patient had developed an anaphylactic reaction to the antibiotic. However, since the patient did not show the typical symptoms of wheezing, urticaria or swelling of the mucous membranes associated with anaphylaxis and had also received the same antibiotic on four previous occasions (for the treatment of *P. aeruginosa* pneumonia) without any problems, we considered other possibilities. A 12-lead electrocardiogram (ECG) was obtained, which showed marked ST elevation in leads II, III and aVF and complete atrioventricular (AV) block (Fig. 1A); a previous 12-lead ECG obtained at the time of admission of the patient for pneumonia a month earlier was normal. Based on the ECG finding of ST-segment elevation, which was suggestive of ischemic heart disease, we consulted our experts from the Department of Cardiology. As the patient had hypotension (systolic blood pressure 60 mmHg), we administered 0.01 mg of epinephrine by intravenous injection and performed rapid-sequence intubation. The blood pressure improved after the patient was initiated on mechanical ventilation. Subsequently, contrast-enhanced chest CT ruled out aortic dissection, and a head CT ruled out intracranial hemorrhage. An emergency coronary angiogram was also obtained, which revealed no obvious stenosis of the coronary arteries (Fig. 2). Also, by this time, the ST-segment elevation on the ECG had normalized (Fig. 1B). Based on this course of events, the patient was diagnosed as having coronary artery spasm as an anaphylactic reaction to TAZ/PIPC (Kounis syndrome type I) and was managed in the Intensive Care Unit (ICU). To maintain the blood pressure, we administered infusions of fluids and noradrenaline (0.04-0.1 μg/kg/min). In addition, we also administered an H2 blocker (famotidine 10 mg), a histamine antagonist (D-chlorpheniramine maleate 5 mg), and a steroid (methylprednisolone 60 mg) to treat the anaphylactic reaction, and the antibiotic to treat the bacterial pneumonia was switched from TAZ/PIPC to levofloxacin (LVFX). Fifteen

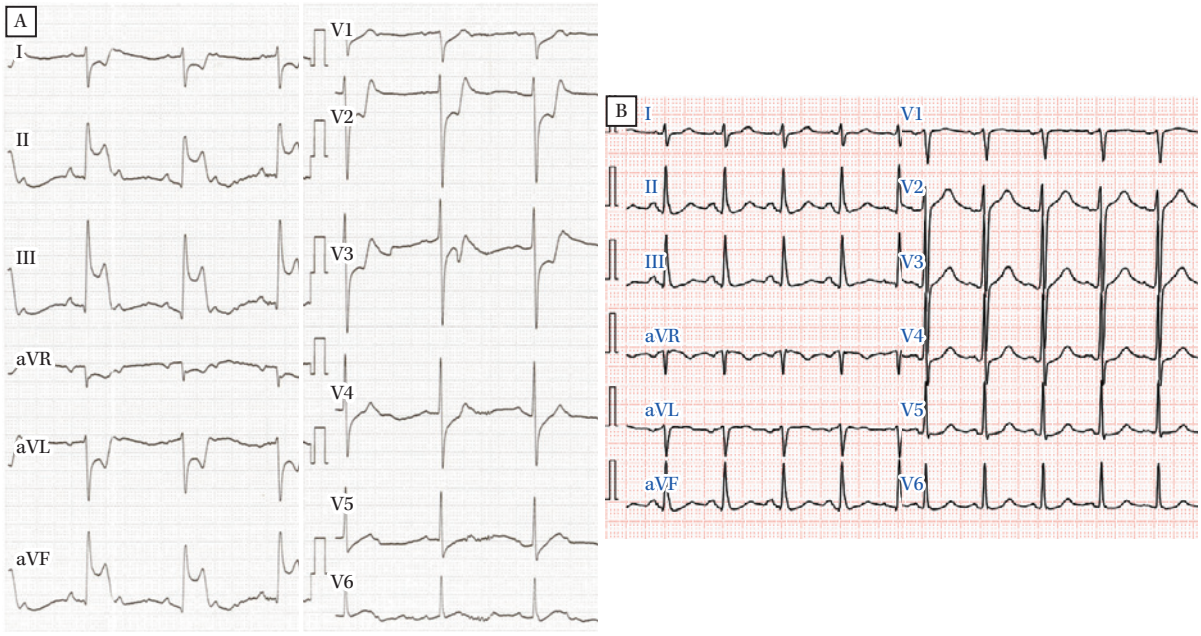

Fig. 1. (A) A 12-lead ECG obtained immediately after the administration of tazobactam/piperacillin and subsequent loss of consciousness, showing ST-segment elevation in leads II, III, and aVF, and ST-segment depression in leads I, aVL, V2, and V3 (with reciprocal depressions in leads I and aVR). Complete atrioventricular block was also suspected from the ECG findings. (B) After aggressive fluid resuscitation, low-dose epinephrine administration, and initiation of intubation and ventilatory support, the ST-segment elevations and other ECG changes normalized.

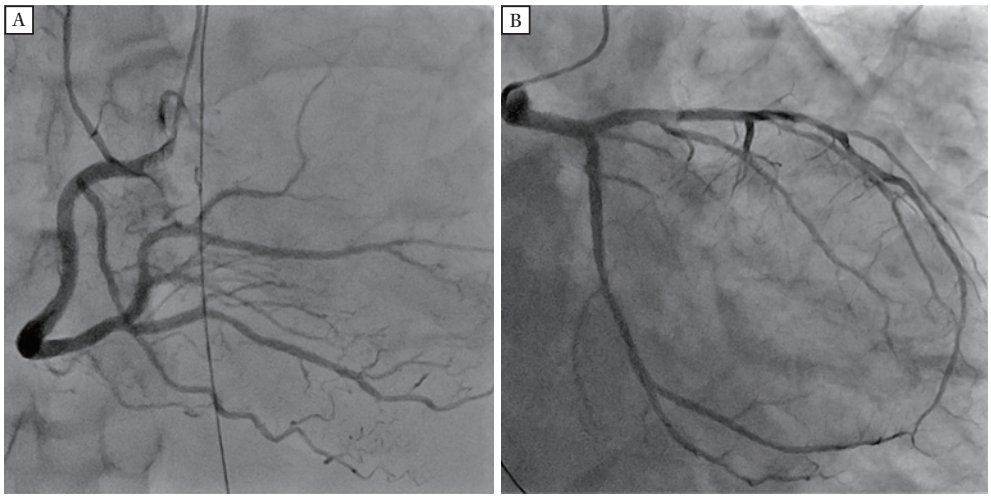

Fig. 2. Coronary angiographic images showing no significant stenosis in the (A) right and (B) left coronary arteries.

minutes after the patient received methylprednisolone, the blood pressure dropped again, with a repeat ECG showing mild ST-segment elevation in leads II, III, and aVF (data not shown). Given the patient's history of diclofenac sodium-induced urticaria and the possibility of methylprednisolone sodium succinate-induced allergic reaction, we discontinued the methylprednisolone and switched the steroid to dexamethasone (6 mg) and the antibiotic to intravenous LVFX 500 mg. Subsequently, the patient's vital signs, overall condition, and respiratory status stabilized, and the ST-segment ele-

vation observed on the 12-lead ECG improved. By 20 hours after admission to the ICU, the patient could be weaned from the ventilator and extubated. On day 2 after extubation, the patient was transferred to a general ward, and after 7 days, the antibiotic therapy was discontinued. A repeat blood test after the patient was discharged from the ICU revealed an elevated serum IgE level (229 IU/mL). Drug-induced lymphocyte stimulation test (DLST) was performed for TAZ/PIPC and methylprednisolone, but the results were negative. Although we considered prescribing an epinephrine autoinjector (EpiPen®) for prophylaxis, we decided against it due to concerns about potential coronary spasm. Benidipine 4 mg/day was prescribed for the prevention of coronary spasm. The patient was discharged on the 11th day of hospitalization. Future antibiotic therapy will be determined based on the patient's clinical progress; however, it was decided that β-lactam antibiotics will be avoided where possible and LVFX used instead.

III. Discussion

Anaphylaxis is the most severe clinical manifestation of acute systemic allergic reactions. Anaphylaxis is highly likely when at least one of the following two criteria is fulfilled[4]:

1. Acute onset of illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both.
2. Acute onset of hypotension, bronchospasm, or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to a few hours), even in the absence of typical skin involvement.

The condition of the patient reported herein met the aforementioned Criterion 2, and we diagnosed the patient as having an anaphylactic reaction. The use of TAZ/PIPC is increasing, and the number of cases suspected as being allergic to this preparation is also rising. It has been reported that many false-negative skin tests occur for allergies to TAZ/PIPC[5]. This is consistent with the condition of our patient, who showed no skin rash.

In addition, in a report of four cases of anaphylaxis caused by methylprednisolone in adult asthma patients, one patient did not manifest a skin rash; that patient had aspirin-induced asthma, which is associated with a risk of sodium succinate allergy[6]. Similarly, in our patient, the patient had a history of urticaria developing following intake of diclofenac sodium. The patient showed a fall of the blood pressure, accompanied by ST-segment elevation in ECG leads II, III, and aVF after receiving methylprednisolone injection. Therefore, we considered the possibility of Kounis syndrome involving succinic acid allergy. Other potential causes of the reaction that we considered included a biphasic anaphylactic reaction to TAZ/PIPC. Because the effects on the circulatory system are significant and acute circulatory deterioration can occur, it is thought that a skin rash may not manifest easily. Our patient showed a negative reaction of the DLST for both drugs; however, since this test is specific for type IV allergies, it was considered difficult to pinpoint the causative drug in this case.

Kounis syndrome is classified into three types. Type I involves coronary artery vasospasm in patients without significant pre-existing coronary artery disease. Type II is characterized by rupture of an existing atherosclerotic plaque, leading to acute coronary syndrome. Type III occurs when in-stent thrombosis develops in patients with prior coronary stent implantation. The type in our patient anaphylactic shock following was considered as type I. The annual incidence of Kounis syndrome among emergency medical patients treated for anaphylaxis is reported to be 3.4%[7]. The most frequently implicated culprit drugs were antibiotics, as in our patient, followed by non-steroidal anti-inflammatory drugs (NSAIDs), antineoplastic agents, and contrast media[1]. There is no specific test to diagnose Kounis syndrome; the clinical diagnosis is based on identifying signs and symptoms of an allergic reaction and signs along with symptoms of an acute coronary syndrome[8]. Most patients with Kounis syndrome present with skin

symptoms, bronchospasm, or anaphylaxis. In a study of 175 patients with Kounis syndrome, 87% had chest pain, more than 95% had abnormal ECG findings, and the most common finding was ST-segment elevation[9]. Our patient did not have chest pain, only nausea, and there was no urticaria or wheezing, which is atypical for Kounis syndrome[9]. Despite our patient not complaining of chest pain, the prompt and accurate diagnosis by the emergency room physician and cardiologist was considered as having contributed significantly to the favorable outcome in our patient. This patient also had a history of receiving treatment with TAZ/PIPC for pneumonia on four previous occasions, so that we did not initially consider allergy to this antibiotic as a strong possibility in our patient. However, literature suggests that anaphylaxis can occur even with drugs that have been used safely in the past[10]. In fact, in a literature report of Kounis syndrome developing after TAZ/PIPC administration, Kounis syndrome occurred after the second administration of the drug for bacterial pneumonia[11]. Therefore, it is necessary to always be careful about the possibility of allergic reactions to antibiotics, even after the first administration.

Treatment of Kounis syndrome is challenging, because the clinical manifestations of allergic reactions and acute coronary syndrome are highly diverse. It is necessary to carefully balance and consider the effects of cardiovascular medications on both anaphylaxis and the coronary syndrome. In particular, adrenaline/epinephrine, which is the key drug to reverse anaphylaxis, can induce coronary vasoconstriction, decrease coronary blood flow, increase myocardial oxygen demand, and potentially worsen myocardial ischemia. Therefore, it has been reported that starting with small doses of epinephrine and adjusting the dosage as appropriate is advisable in cases of Kounis syndrome[12]. In our patient, we administered 0.01 mg of epinephrine by intravenous injection, which was sufficient to increase the blood pressure to an appropriate level. Additionally, we infused large volumes of fluid and norepinephrine to stabilize the patient's blood pressure.

Our patient experienced recurrent hypotension due to anaphylactic shock following administration of methylprednisolone. Given the patient's documented allergy to diclofenac sodium, we considered the possibility of succinic acid allergy and switched the steroid from methylprednisolone to betamethasone. In addition, we administered benidipine, a calcium channel blocker, to prevent coronary spasm[13]. Following this intervention, the patient developed no further recurrence of symptoms.

In summary, this is a report of a rare patient with TAZ/PIPC -induced Kounis syndrome, with similar symptoms also triggered by therapeutic administration of methylprednisolone sodium succinate. The patient's life was saved by timely ventilatory management, including intubation and mechanical ventilation. Anaphylaxis can occur even after multiple doses of a drug have been administered safely before, and rapid evaluation is necessary. Furthermore, simultaneous management of allergic reactions and acute coronary syndromes is crucial, requiring a careful consideration and balancing of the effects of cardiovascular agents on both anaphylaxis and coronary artery lesions during drug selection and administration.

Authorship statement

All authors meet the ICMJE authorship criteria. All authors have seen and approved the final version of the manuscript and contributed significantly to the work. All authors contributed to the writing of the final manuscript.

Declaration of Competing Interests

There are no conflicts of interest to report in relation to this study.

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Patient consent for publication

The patient provided written informed consent for publication of this report.

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