

Allergic Acute Coronary Artery Stent Thrombosis After the Administration of Sugammadex in a Patient Undergoing General Anesthesia: A Case Report

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In addition to cutaneous, gastrointestinal, hemodynamic, and respiratory symptoms, allergic reactions can induce an acute coronary syndrome in normal or atheromatous coronary arteries and can cause coronary stent thrombosis. Here, we report a case of coronary stent thrombosis due to allergic acute coronary syndrome during anaphylaxis induced by sugammadex in a female patient undergoing general anesthesia. She was emergently treated with percutaneous transluminal coronary balloon angioplasty with catecholamine, vasodilator, and intraaortic balloon support. Knowledge of perioperative allergy-triggered acute coronary syndrome is crucial for prompt and appropriate treatment. (A&A Practice. XXX;XXX:00–00.)

Allergic reactions contribute to 3%–4% of perioperative coronary artery spasms.¹ Allergic acute coronary syndrome can occur under general, epidural, or spinal anesthesia.^{1,2} In the setting of allergic or hypersensitivity reactions, antigen–antibody reaction, mast cell activation, and histamine release play an essential role in coronary vasoconstriction and platelet activation. Kounis³ classified allergic coronary reactions into 3 types: type I—coronary spasm without coronary artery disease; type II—coronary spasm or plaque rupture with coronary artery disease; and type III—coronary artery stent thrombosis.

Sugammadex, a reversal agent of muscle relaxant, has recently emerged as a causative agent for anaphylaxis,⁴ allergic coronary spasms,⁵ and sudden cardiac arrest^{6,7} and can even be fatal.⁷ Here, we report a case of allergic coronary stent thrombosis (type III) caused by sugammadex under general anesthesia. To the best of our knowledge, this is the first case report of perioperative allergic intrastent thrombosis.

Written informed consent for the use of medical records was obtained from the patient and family at hospital admission. This case report was approved by the Institutional Review Board of the Committee of Ethics in Hamamatsu Rosai Hospital (Hamamatsu, Japan).

DESCRIPTION OF THE CASE

A 71-year-old woman was scheduled for an elective laparoscopic right hemicolectomy for colon cancer. She had an American Society of Anesthesiologists physical status of III, weight of 57 kg, and a body mass index of 25.3. One month before the surgery, she experienced

non-ST-segment-elevation myocardial infarction and underwent percutaneous transluminal coronary balloon angioplasty. Drug-eluting stents were placed in the proximal and middle right coronary arteries. Her medical history was significant for anemia (hemoglobin, 10.0 g/dL), hypertension, diabetes mellitus, but no known drug allergies.

Seven days before the hemicolectomy, clopidogrel was discontinued and replaced with a continuous infusion of heparin, which lasted until 4 hours before surgery. Aspirin was given for 1 month, from the time of drug-eluting stent implantation to the day before surgery, as defined by Japanese standard regimens for major surgery. The regimens are based on a Japanese population-based observational study⁸ which indicated that the discontinuation of clopidogrel alone was not associated with an increased risk of stent thrombosis at 1–6 months after drug-eluting stent implantation.

After application of standard monitors, a continuous infusion of 2 mg/h nicorandil (ATP-sensitive potassium [K_{ATP}] channel opening and nitrate-like actions) was initiated for coronary vasodilation before anesthesia induction. The patient's preoperative heart rate (HR) and cuff blood pressure were 88 bpm and 162/46 mmHg, respectively. General anesthesia was induced with propofol (50 mg), fentanyl (100 μ g), and rocuronium (40 mg) and was maintained after uneventful tracheal intubation with oxygen, air, 3% desflurane, fentanyl, remifentanyl (0.05–0.15 μ g/kg/min), and boluses of rocuronium. A train-of-four response and posttanic contractions were monitored in the ulnar nerve. The arterial blood pressure was monitored with a radial artery catheter. Cefmetazole (1 g) was administered before the start of surgery. The 4-hour intraoperative course was uneventful. At the end of surgery, 0.5% bupivacaine (20 mL) was used for local infiltration analgesia in the umbilical wound. The patient received the total dose of fentanyl (425 μ g), remifentanyl (1.6 mg), and rocuronium (100 mg).

The patient recovered spontaneous ventilation and 1–2 twitches of 4 twitches in the train-of-four response. Then, 100 mg of sugammadex was administered, desflurane was discontinued, and the patient was extubated breathing 100% O₂. Approximately 10 minutes after sugammadex administration, the patient complained of generalized pruritus and urticaria (Figure 1). Figure 1 presents the changes

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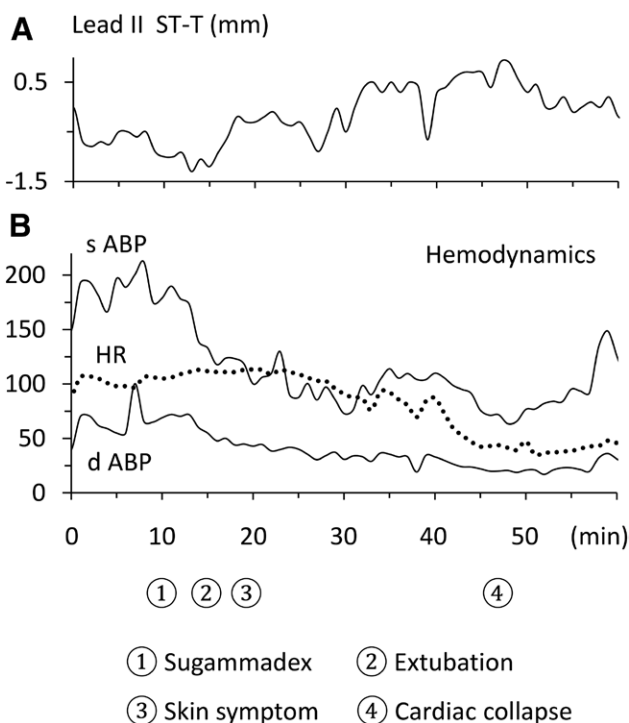


Figure 1. The changes in electrocardiography and hemodynamics around the time of allergic events. The changes in ST-T in lead II are presented in (A), and the changes of HR (beat/min, dotted line) and radial arterial blood pressure (mmHg, solid lines) are presented in (B). Time 0 indicates 10 min before sugammadex administration. dABP indicates diastolic arterial blood pressure; HR, heart rate; sABP, systolic arterial blood pressure.

in ST-T in lead II of electrocardiography, HR, arterial blood pressure, and patient's symptoms and events around the time of allergic reactions. She had tachypnea (20 breaths/min), but no wheezing or dyspnea.

An allergic reaction was suspected, and she was administered famotidine (20mg), hydrocortisone (100mg), and stronger neo-minophagen C (20mL; glycyrrhizin, glycine, cysteine combined antiallergic agents). Her HR and radial arterial pressure dropped suddenly to 30 bpm and 60/25 mmHg, respectively. Atropine (0.75mg) and ephedrine (8mg) were administered. A cardiologist was urgently called and norepinephrine was initiated at 0.06 µg/kg/min according to the therapeutic guideline for acute coronary syndrome, because we assumed that bradycardia and hypotension were primarily caused by acute myocardial ischemia, which was preceded by allergic reaction. ST-T elevation in lead II and atrial ventricular block with an escape rhythm were observed. In addition to anaphylactic shock due to sugammadex, subsequent acute heart failure due to right coronary arterial perfusion insufficiency was suspected.

Acute myocardial infarction in the inferior wall was suggested by chest 12-lead electrography (Figure 2). Echocardiography revealed no wall motion abnormality and an ejection fraction of 62% (M-mode method). Emergency coronary angiography revealed stent thrombosis in the middle of the right coronary artery with 100% occlusion; however, the thrombus could not be aspirated. Therefore, balloon angioplasty was conducted and reperfusion was

successful (Figure 3). Ventricular fibrillation occurred twice during coronary intervention and was successfully defibrillated. After the placement of an intraaortic balloon pump, the patient was transferred to the intensive care unit. The creatine phosphokinase myocardial band (CPK-MB) peaked at 191 U/L (normal level, <25 U/L).

The patient recovered uneventfully and was discharged from the hospital 35 days postoperatively without discernible sequelae. We did not measure the level of tryptase or histamine. She chose not to undergo a skin test because she and her family were afraid of harmful allergic reactions. Three years after the surgery, a lymphocyte transformation test (LSI Medience Corp, Tokyo, Japan) for sugammadex was conducted with the patient's consent. The test was positive at 185% (a negative value is <179%). The drug-induced lymphocyte transformation in vitro test proves that the tested drug is responsible for the reaction in subjects previously sensitized to this drug.⁹

DISCUSSION

Allergic acute coronary syndrome is associated with male sex (74.3%), coronary spasm without coronary disease (Kounis type I; 72.6%), ST-T elevation (76%), anaphylaxis (53%), skin symptoms (26.8%), wheezing (14%), and mortality (2.9%).¹⁰ Antibiotics are the most common cause, which are observed in 27.4% of allergic acute coronary syndrome.¹⁰ There are very few perioperative case reports regarding allergic coronary stent thrombosis (Kounis type III), which is observed in only 5.1% of allergic acute coronary syndrome.¹⁰

We gave our patient atropine, ephedrine, and norepinephrine to treat bradycardia and hypotension after the administration of sugammadex. At that time, we and the cardiologists involved in the case believed that hemodynamic collapse was primarily caused by acute coronary syndrome under a preceding allergic reaction. Consequently, we followed the recent acute coronary syndrome guidelines in the present case. In general, we probably should have administered 0.3mg of epinephrine intramuscularly (or 5–10 µg IV) for anaphylactic shock. However, epinephrine should be used with caution in allergic coronary syndrome because it can worsen myocardial ischemia, prolong the QTc interval, and induce coronary vasospasm and arrhythmias.¹⁰ Allergy-induced coronary syndrome is a new clinical entity that is very rarely diagnosed and easily overlooked. Therefore, physicians must have knowledge of allergic coronary syndrome because it is very crucial to provide prompt and appropriate treatments for anaphylaxis and for acute myocardial ischemia.

We could not aspirate the intrastent thrombus to demonstrate intrastent infiltration of eosinophilia and mast cells as evidence of an allergic reaction. Preoperative discontinuation of clopidogrel may have been another causative factor for acute stent thrombosis. However, in a large-scale multicenter observational study in Japan,⁸ the incidence of stent thrombosis 1–6 months after drug-eluting stent implantation was 0.08% in the discontinuation of thienopyridine-only group, which was very similar to the incidence of 0.1% in the nondiscontinuation group. Furthermore, perioperative intrastent thrombosis is extremely rare in the

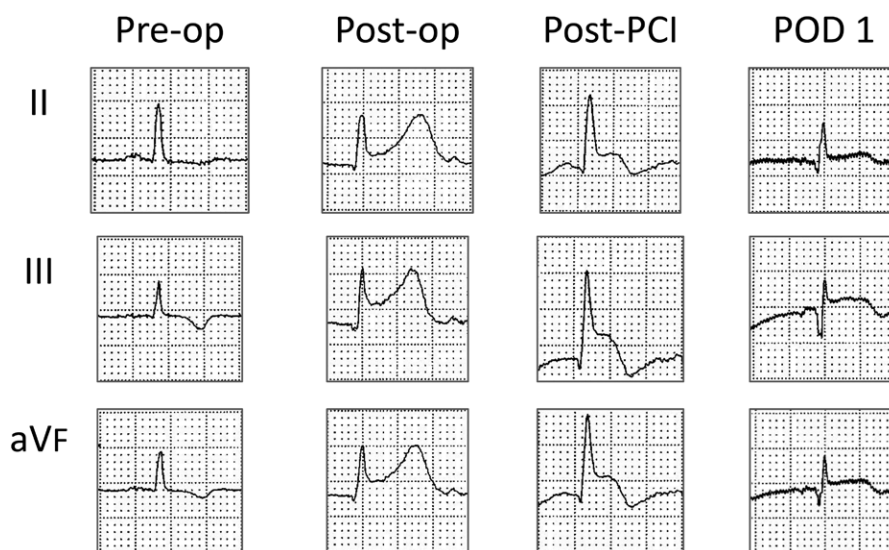


Figure 2. The perioperative changes in ST-T (1mV=10mm) in leads II, III, and aVF of electrocardiography. The patient was diagnosed with acute myocardial infarction in the inferior wall. aVF indicates augmented vector foot; POD1, postoperative day 1; Post-op, postoperative; Post-PCI, postpercutaneous coronary intervention; Pre-op, preoperative.

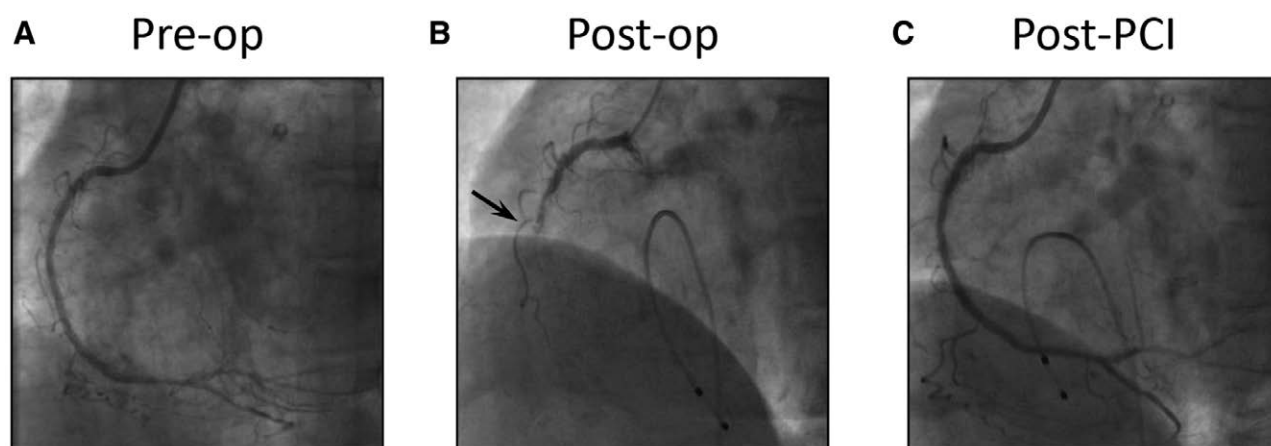


Figure 3. Perioperative changes in right coronary angiography. In contrast to Pre-op (A) right coronary perfusion, postoperative coronary angiography imaging reveals an intrastent thrombosis in the middle of the right coronary artery with 100% occlusion (arrow, Post-op [B]). After balloon angioplasty, reperfusion was successful (Post-PCI [C]). Post-op indicates postoperative; Post-PCI, postpercutaneous coronary intervention; Pre-op, preoperative.

large population studies conducted in the United States (3/215,077 patients) and Japan (0/36,634 patients).^{11,12} Therefore, it is quite unlikely that stent thrombosis independently developed without any influence of a preceding allergic reaction in the present case. In addition, allergic intrastent thrombosis can occur even with the continuation of aspirin and clopidogrel.¹³

The incidence of anaphylaxis associated with sugammadex is 0.039% (1/2500 patients), which is as high as the incidence of anaphylaxis for succinylcholine or rocuronium.⁴ The sugammadex-rocuronium complex can be an antigen and induce coronary vasospasm under anaphylactic shock.⁵ Sugammadex can cause life-threatening or fatal cardiac arrest in patients without cardiac disease.^{6,7} Unlike sugammadex, anaphylaxis induced by neostigmine is extremely rare.¹⁴ Furthermore, in Japan, the cost of sugammadex (100–200 mg: 2–4 mg/kg for weight of 50 kg, approximately \$40–80) is 8–16 times higher than a total cost of neostigmine (2 mg) and atropine (1 mg) (approximately \$5). If a patient receives careful monitoring for neuromuscular function with acceleromyography and recovers adequate

spontaneous breathing before extubation, neostigmine appears to be safer and more cost-effective than sugammadex. Indeed, data from a recent large multicenter prospective observational study did not show any advantage of sugammadex over neostigmine with respect to pulmonary outcome.¹⁵ Sugammadex can cause life-threatening anaphylaxis and allergic acute coronary syndrome including coronary stent thrombosis. Therefore, sugammadex should be carefully considered, especially in patients with cardiac comorbidities, unless you can demonstrate legitimate benefits over neostigmine when fatal cardiac accidents occur. ■

DISCLOSURES

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