

Kounis Syndrome or Allergic Coronary Vasospasm in a Two-year-old

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ABSTRACT

Kounis syndrome is coronary vasospasm because of mast cell degranulation in the context of an allergic reaction. The syndrome has known associations with several drugs used during anesthesia, including rocuronium and isoflurane. In this case report, we discuss a 2-year-old patient who developed signs and symptoms of an acute coronary syndrome soon after anesthesia for atrial septal defect repair. A diagnostic angiography after the episode revealed diffusely small coronary arteries. Subsequent angiography after clinical improvement showed essentially normal coronary anatomy. We report the clinical course of this patient and postulate that Kounis syndrome was the explanation for his transient coronary vasospasm. To date, this is the youngest known patient with reported Kounis syndrome.

Key Words. Kounis Syndrome; Allergic Angina; Coronary Vasospasm; Mast Cell; Rocuronium; Isoflurane; Children; Cardiac Surgery

Introduction

Kounis syndrome, or “allergic angina,” is an acute coronary syndrome (ACS) associated with mast cell activation because of allergy, hypersensitivity, or anaphylaxis. Mast cell mediators can trigger angina or myocardial infarction by acting on vascular smooth muscle to promote coronary vasospasm or by directly disrupting atheromatous plaques. Kounis syndrome has been associated with many atopic conditions, drug allergies, and environmental allergies.¹ The syndrome has been associated with the neuromuscular blocking agent rocuronium and the inhalational anesthetic isoflurane, among other drugs.^{2,3} Here, we discuss the case of a 2-year-old boy with apparent Kounis syndrome, possibly because of these two drugs. To the best of our knowledge, this is the youngest patient with Kounis syndrome reported in the literature.

Case Report

During a routine physical examination, a 2-year-old boy was found to have a fixed split of the second heart sound and an echocardiogram revealed a large secundum atrial septal defect (ASD), with moderate right atrial and right ventricular dilatation. The remainder of his physical

examination and medical history was unremarkable, except for a history of frequent atopic symptoms, including eczema and hives in reaction to certain foods and “emotional stress.”

The patient underwent surgical repair of the ASD with autologous pericardium. His preoperative medications included cefazolin, midazolam, fentanyl, rocuronium, and continuous inhaled isoflurane. Total cardiopulmonary bypass (CPB) was 41 minutes. During the rewarming phase of the CPB, his electrocardiogram (ECG) showed significant intermittent periods of diffuse ST segment elevation, but by the end of the case, the ST changes had subsided. The patient was extubated in the operating room, and was placed on dexmedetomidine infusion for sedation/analgesia and low-dose epinephrine (0.03 mcg/kg/min) for mild hypotension. He was transferred to the cardiac intensive care unit (ICU).

Within 4–6 hours off CPB, he developed an increased oxygen requirement because of pulmonary edema. Continuous telemetry showed recurrent and transient ST elevation. This was confirmed by a 12-lead ECG that showed diffuse ST depression (Figure 1). The troponin level at the time was elevated at 18.3 ng/mL. Because of worsening cardiorespiratory status, he required



Figure 1. Postoperative electrocardiogram demonstrating diffuse segment depressions.

re-intubation and was given rocuronium and fentanyl. Echocardiogram now showed moderately decreased biventricular systolic function. Within 2 hours, he again developed significant and transient ST depression, now associated with worsening pulmonary edema, bradycardia, and hypotension to 57/36 mm Hg. Inotropic support was increased and after stabilization, patient was transferred to the cardiac catheterization lab for diagnostic angiography. Before the procedure started, the patient developed significant ST elevation, hypotension, and bradycardia necessitating initiation of cardiopulmonary resuscitation (CPR). Though spontaneous circulation returned, due to ongoing instability, he was placed on extracorporeal membrane oxygenation (ECMO). Subsequently, coronary angiography revealed diffusely small left and right coronary artery systems without apparent response to nitroglycerin (Figure 2A). While the patient was on ECMO support, all other hemodynamic data obtained were unremarkable. At this point, because of lack of a better alternative, the presumptive diagnosis was “congenital hypoplasia of the coronary arteries,” carrying a rather grim prognosis.

After 3 days, the patient was converted from ECMO to a Berlin type biventricular assist device (BiVAD) and was evaluated for heart transplantation. Myocardial biopsy obtained during the BiVAD placement was unremarkable.

Of particular note are some of his extracardiac complications. Thirty-six to 48 hours after his initial decompensation, he developed profound anuric renal failure requiring hemodialysis for 13 days and compartment syndrome of his right calf requiring fasciotomy and multiple debridements. Although these types of complications can occur in patients after cardiac arrest, the severity of these two complications was somewhat unexpected, given that the event was a witnessed arrest with immediate CPR and lack of significant lactic acidosis. The peak lactic acid during the peri-arrest period was only 3.5 mmol/L. Other transient but significant complications involved bilateral cerebral watershed infarcts associated with seizure activity, and acute respiratory distress syndrome requiring mechanical ventilation for 21 days. Gradually, over the following few weeks, his mental status and multiple organ system dysfunction improved, and he became a candidate to be placed on the list for heart transplantation.

Interestingly however, during these few weeks of recovery, serial echocardiograms showed that there was a gradual and steady improvement in his biventricular function. The first noticeable improvement was seen 7 days after the BiVAD was placed. Given the fact that this and subsequent echocardiograms were performed with the patient on full BiVAD support, it was very difficult to

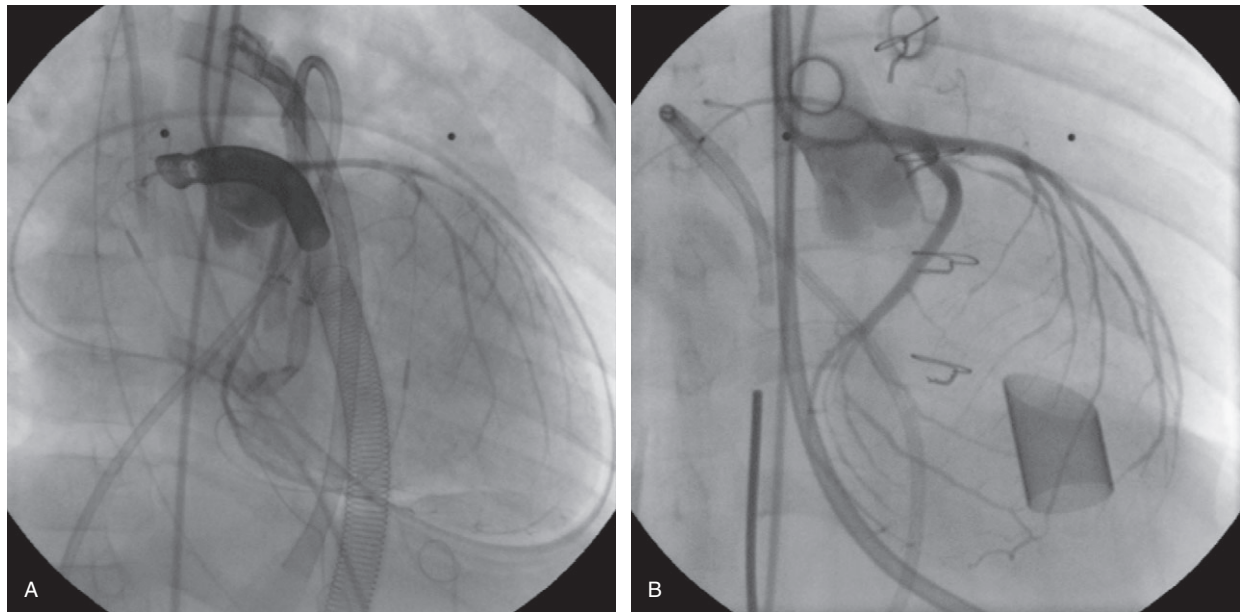


Figure 2. (A) Postoperative coronary angiogram demonstrating diffuse narrowing in both right and left coronary artery systems; (B) Coronary angiogram in the same patient 1 month later demonstrating resolution of prior narrowing.

differentiate between an actual improvement in the ventricular function vs. an “echocardiographic” improvement seen with unloaded ventricles when patients are placed on BiVAD support. Nevertheless, because of the steady improvement and with what appeared to be a normal echocardiographic biventricular systolic function 1 month after the initial event, the decision was made to obtain another cardiac catheterization to reevaluate the coronary arteries. The angiography at this time essentially showed normal right and left main coronary artery systems without significant stenosis other than mild narrowing of the obtuse marginal coronary which improved after administration of nitroglycerin (Figure 2B). At this time, the possibility of Kounis or Kounis-like syndrome with an anaphylactic event causing reversible coronary vasospasm was suspected.

Two days later, the patient was taken back to the operating room for the BiVAD removal. Although he received a preemptive perioperative nitroglycerin infusion for this procedure, he again developed intermittent ST changes, which was less prominent than his first episode. Immediately after BiVAD removal, echocardiogram revealed only mild hypokinesis of the left ventricle and near normal function of the right ventricle. Pertinent laboratory work up showed a troponin level of 2.5 ng/mL, a tryptase level of 10 ng/mL (normal <1 ng/mL), immunoglobulin E level of 152 units/mL (normal <60 units/mL), and a histamine

level of 0.3 (normal <1.4). Because of a high clinical and laboratory suspicion of Kounis syndrome, the patient was started on an antihistamine (famotidine) and a mast-cell stabilizer (cromolyn sodium). Nitroglycerin infusion was slowly weaned off and 8 days later, he was discharged from the cardiac ICU. While reviewing his procedures and attempting to identify common culprit medications, which could have induced an allergic coronary vasospasm, we found that he received both rocuronium and isoflurane with every anesthesia. Unfortunately, testing to confirm allergy to these agents was unavailable at our institution.

One year later, the patient remained free of any hospitalizations, with an echocardiogram showing an ejection fraction of 64%. He continues to be on famotidine and cromolyn sodium.

Discussion

Kounis syndrome is an ACS caused by mast cell degranulation in the context of an allergic insult. Type I Kounis syndrome occurs when allergic mediators induce vasospasm in normal coronary arteries without predisposing factors for coronary artery disease. The pediatric population almost invariably experiences the Type I Kounis syndrome. Type II Kounis syndrome occurs when allergic mediators induce plaque erosion and acute myocardial infarction in patients with quiescent atheromatous disease.¹

Mast cells respond to antigens and cross-linked IgE antibodies by releasing compounds that are both vasoconstricting and collagen degrading. Mediators released include tryptase, chymase, histamine, arachidonic acid products, platelet-activating factor, and cytokines. Histamine directly stimulates smooth muscles to produce vasospasm and also acts as a platelet activator, an inducer of cytokine release, and an up-regulator of P-selectin and tissue factor on the endothelium. Tryptase constitutes 20% of the total protein in mast cells and activates metalloproteinases, like collagenase and gelatinase, which contribute to atheroma lysis and rupture. Chymase, another enzyme released by mast cells, also cleaves angiotensin I to angiotensin II, which potentially exacerbates the vasospasm triggered by histamine.^{1,4} In sum, the mast cell milieu creates procoagulant, vasospastic and thrombogenic effects.

Mast cell mediators may play an etiologic role in classic ACS as well. Evidence shows that serum histamine levels are, on average, two times higher in ACS patients than in controls.⁵ If patients experience ST changes, serum tryptase levels are also elevated. Moreover, mast cells were previously postulated to be part of the postinflammatory reaction in ACS, but recent empiric evidence shows that mast cells invade vulnerable coronary plaques and release inflammatory compounds *before* plaque rupture occurs.⁶ This indicates that mast cell mediators may be contributing etiologic factors in ACS. Atopic patients are at higher risk for ACS than normal controls and men with increased IgE levels also have increased incidence of myocardial infarction.^{1,6} Finally, recent data has shown that thrombosis in drug-eluting stents is linked to hypersensitivity and may share a common pathophysiologic pathway with the Kounis syndrome. Hypersensitivity suppressive agents have been proposed to prevent future in-stent thromboses.⁷

Many different conditions, drugs, and substances have been associated with the Kounis syndrome.¹ Particular anesthetic drugs known to cause mast cell degranulation include isoflurane, rocuronium, midazolam, succinylcholine, remifentanyl, and propofol. When more than one of these drugs is used concurrently, it is thought that small doses of each drug act synergistically to cause direct mast cell degranulation.^{1,8,9} Neuromuscular blocking agents, especially rocuronium and succinylcholine, are the most common agents during anesthesia that causes anaphylaxis, and have known associations with Kounis syndrome.²

Diagnostic evaluation for Kounis syndrome includes assays for cardiac enzymes, troponins, histamine, tryptase, and IgE levels. Although elevated tryptase level has a reported sensitivity of 73% and specificity of 98% in diagnosing anaphylaxis, the half-life of tryptase is only 90 minutes. Histamine has an even shorter half-life of 8 minutes. Therefore, the best time to measure levels is 1–2 hours after the ACS event. Normal histamine and tryptase levels which are drawn after this time period do not rule out the diagnosis of Kounis syndrome.^{4,9,10}

The patient described in this case report likely experienced Type I Kounis syndrome because of an allergic reaction to rocuronium and isoflurane. This is the most likely diagnosis because: (1) after each of the three times he received rocuronium and isoflurane, he exhibited classic signs of myocardial ischemia with ECG changes, hemodynamic instability, and troponin elevations; (2) during his prolonged ICU stay, he did not exhibit signs of ischemia after his multiple other surgeries and procedures which used alternative anesthetic agents; (3) coronary arteries were diffusely and severely narrowed after his second exposure to rocuronium, but were normal on follow-up angiogram 1 month later, consistent with transient vasospasm; (4) after the third ischemic attack, total IgE was three times above normal and tryptase was 10 times above normal, consistent with diffuse mast cell activation; and (5) he has an atopic history which could have predisposed him to Kounis syndrome. The only piece of data not consistent with the Kounis syndrome is his normal histamine level obtained later that week. However, as noted previously, the half life of histamine is short and would be expected to be within the normal range at the time it was assayed.

Mast cell stabilizers, antihistamines, and steroids may effectively prevent recurrence of the Kounis syndrome. Options include nedocromil, cromolyn sodium, ketotifen, lodoxamine, diphenhydramine, famotidine, or prednisolone. Such agents may eventually be used prophylactically before anesthesia induction of patients with an atopic history or may even be used as new therapeutic agents to prevent ACS.^{1,2,10}

In conclusion, although it is rare, allergic coronary artery vasospasm or Kounis syndrome, leading to myocardial ischemia and infarction can occur in the pediatric population. Awareness of this syndrome is crucial because the coronary insult can be transient and may respond to mast cell stabilizers. Although Kounis syndrome has been previously

reported in the pediatric population, this current case represents the youngest patient so far.¹⁰

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