

## *Kounis Syndrome: A simple MRI with contrast turned into a life threatening condition*

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### ABSTRACT

Kounis syndrome (KS) is a hypersensitivity coronary disorder induced by various allergens. It is a rare condition which has been reported in every age group (2-90 years) and in every race and geographic location. Its incidence has been reported to range from 7.9 to 19.4 per 100,000. The presentation of the detrimental effects of KS on coronary arteries ranges from vasospastic angina to allergic myocardial infarction. Drugs are the major iatrogenic cause of KS, but virtually everything in the environment around us can cause KS. In recent years contrast mediums used in the radiologic investigation have come forth as a leading cause of anaphylaxis. Gadolinium is a rare earth metal that is used in contrast mediums for magnetic resonance imaging and is generally considered to be safe.

This is a case of 52-year-old female who developed KS after receiving gadobenate dimeglumine, a gadolinium based contrast medium (GBCM) for MRI of the brain as a work up for metastatic renal cell carcinoma. Her EKG was remarkable for ST elevations in the inferior leads. Cardiac catheterization was performed which did not reveal any significant obstructive coronary artery disease. Patient was treated with anti-histamines, corticosteroids and norepinephrine after which she recovered and discharged home stable. GBCM induced KS is very rare and to our knowledge this is the third case of Kounis syndrome reported in association with gadobenate dimeglumine.

### KEYWORDS

Kounis, Acute coronary syndrome, Coronary spasm, Anaphylaxis, MRI, Gadolinium

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### INTRODUCTION

Coronary vasospasm is referred to as constriction of coronary arteries that causes complete occlusion or near to complete occlusion of an artery leading to decreased blood flow to the myocardium.<sup>1</sup> Anaphylaxis is an immediate allergic reaction that has the propensity to cause severe coronary vasospasms.<sup>2,3</sup> Anaphylaxis virtually affects all major systems of the body including the cardiovascular system making the heart a target organ.<sup>4</sup>

Kounis syndrome is a hypersensitivity coronary disorder induced by various allergens.<sup>5</sup> It is a rare condition which has been reported in every age

group (2-90 years) and in every race and geographic location. Its incidence has been reported to range from 7.9 to 19.4 per 100,000.<sup>5</sup> In response to an allergen, inflammatory cells secrete mediators such as histamine and tryptase causing changes to the systemic and coronary vasculature. The presentation of the detrimental effects of KS on coronary arteries ranges from vasospastic angina to allergic myocardial infarction.<sup>5</sup>

Drugs are the major iatrogenic cause of KS, but virtually everything in the environment around us can cause KS. In recent years contrast mediums used in the radiologic investigation have come forth as a leading cause of anaphylaxis.<sup>6,7</sup> Gadolinium is a



rare earth metal that is used in contrast mediums for magnetic resonance imaging and is generally considered to be safe.<sup>8</sup> Here we report a very rare case of KS in response to gadobenate dimeglumine (a gadolinium based contrast medium), which is to our knowledge the third case of Kounis syndrome reported in association with gadobenate dimeglumine.

## CASE PRESENTATION

A 52-year-old female with no known allergies has past medical history of a unilateral nephrectomy due to renal cell carcinoma years ago and chronic kidney disease (CKD). She was recently diagnosed with locally advanced and recurrent renal cell carcinoma with metastatic lesion to the left lower lung and presented to the radiology department for an MRI brain with contrast. In the MRI suite, the patient was given gadolinium contrast after which she developed severe sub-sternal chest pain and shortness of breath that was associated with nausea and vomiting. Shortly after that she collapsed with systolic blood pressure in the 80s so patient was intubated and given IV fluid boluses. ECG was done immediately and that showed ST elevations in inferior leads (Figure 1) and code heart was called. Right-sided ECG was done which showed right ventricular infarct with ST elevation in V3R-V6R (Figure 2). Troponins were checked by emergency department physician and trended with a peak of 1.12. The patient was emergently transferred to the cath lab where a left heart catheterization was performed which demonstrated that the patient had non-obstructive coronary artery disease with 20% RCA stenosis (Figure 3 & Figure 4); a pulmonary angiogram was also done which ruled out pulmonary embolism (Figure 5). While patient was still on the table of the cath lab, repeat ECG was performed and showed normal sinus rhythm with the resolution of ST-segment elevations (Figure 6).

A diagnosis of Kounis syndrome was made and no percutaneous coronary intervention was performed. The patient was started on norepinephrine, decadron and anti-histamines then transferred to the ICU for further management and observation. During her stay in the ICU, she was weaned off epinephrine

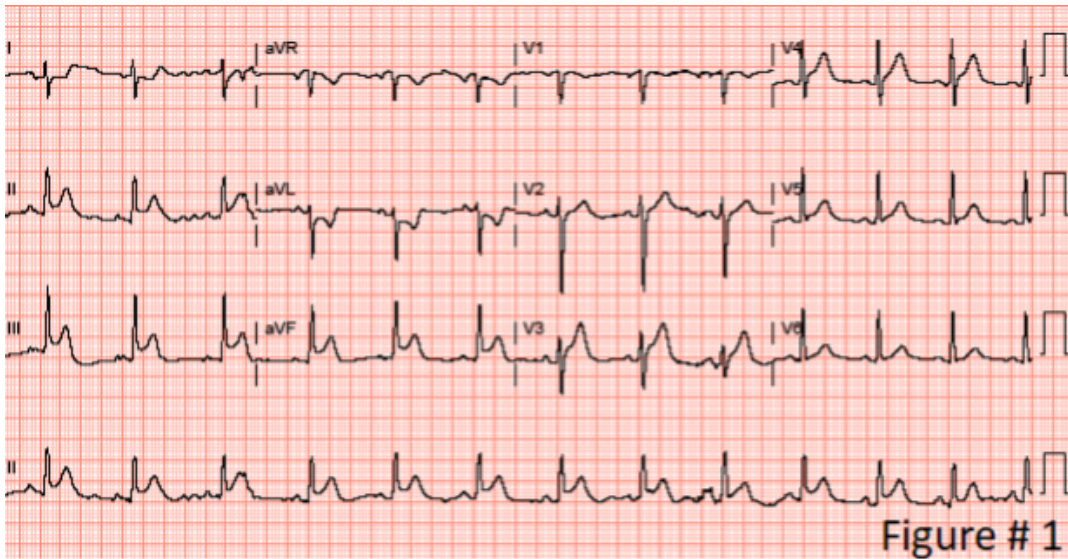
infusion and continued on scheduled decadron. The patient showed signs of improvement and was eventually extubated on the second day of hospital stay. An echocardiogram was performed which showed an ejection fraction of 60-65% with no wall motion abnormality and normal right ventricular size and function. The patient remained stable and was transferred out to the floor and observed for a day, after which she was discharged home.

## DISCUSSION

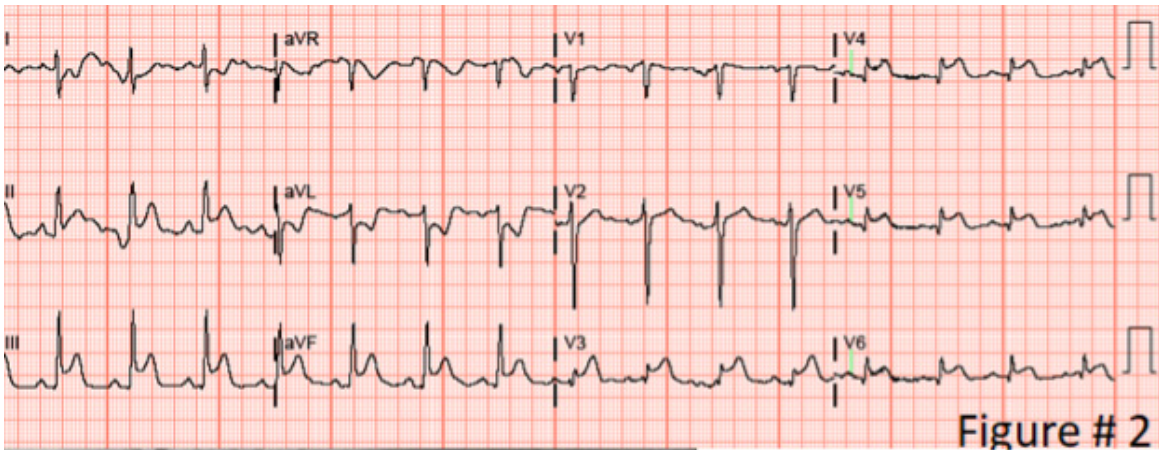
Myocardial infarction is often associated with occlusive coronary artery disease (CAD) but myocardial infarctions in presence of non-obstructed coronary arteries have been reported to be as high as 6%.<sup>9</sup> Coronary artery spasm is attributed to be a major cause for the acute coronary syndrome (ACS) associated with non-obstructed coronary arteries.<sup>9</sup> In 1991, Dr. Nicholas Kounis defined Kounis syndrome [KS] as the occurrence of acute coronary syndrome in the presence of an allergic reaction.<sup>10</sup> KS has three types: (i) Vasospastic allergic angina-ACS in patients with no underlying CAD, (ii) Allergic myocardial infarction-ASC in patients with underlying CAD and (iii) Stent thrombosis with occluding thrombus infiltrated by eosinophils-ACS in patients with established coronary thrombus and stenting. In 2016 the definition of KS was revised to: the concurrence of acute coronary syndromes including coronary spasm, acute myocardial infarction, and stent thrombosis, with conditions associated with mast-cell and platelet activation and involving interrelated and interacting inflammatory cells, such as macrophages and T-lymphocytes, in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults.<sup>5</sup>

Anaphylaxis is referred to as an immediate allergic reaction and or hypersensitivity type reaction. It clinically presents with hemodynamic instability and respiratory compromise; these entail hypotension, tachycardia, bronchospasm, rhinorrhea, conjunctivitis, vasogenic edema, and pruritus.<sup>4,6,7</sup> Although the exact mechanism is yet to be defined, general consensus encompasses release of vasoactive mediators that include namely histamine, serotonin, kinins and prostaglandins.<sup>4</sup> Gueant-

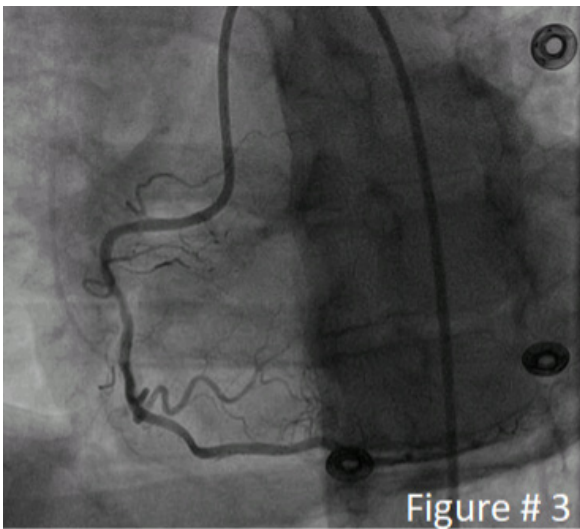




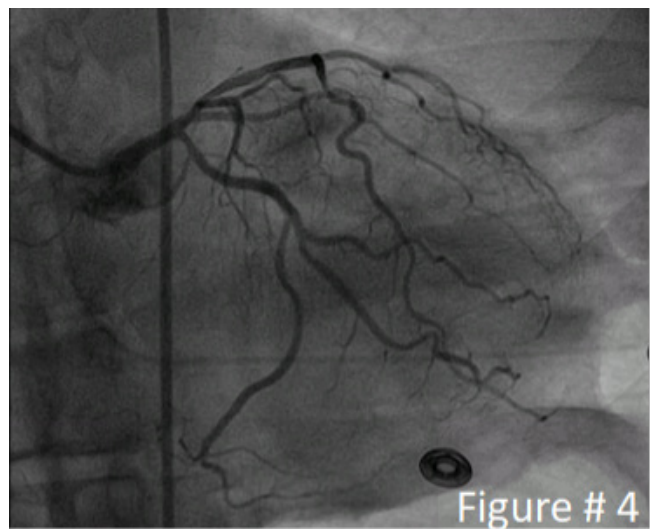
**FIGURE 1** EKG on Presentation - ST II, III, AVF- Inferior Leads – STEMI



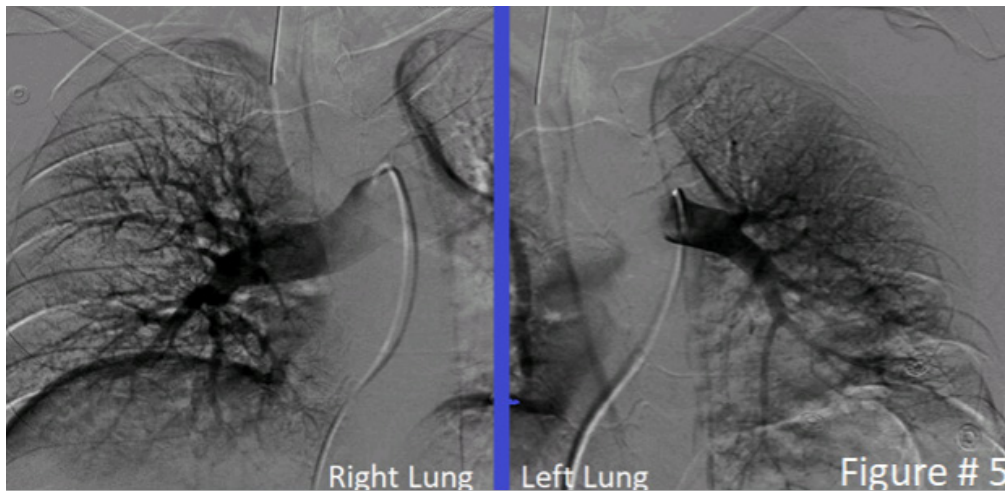
**FIGURE 2** Right Sided EKG, ST elevation in Leads V3, V4, V5, V6 and II, III, AVF with reciprocal changes in aVL



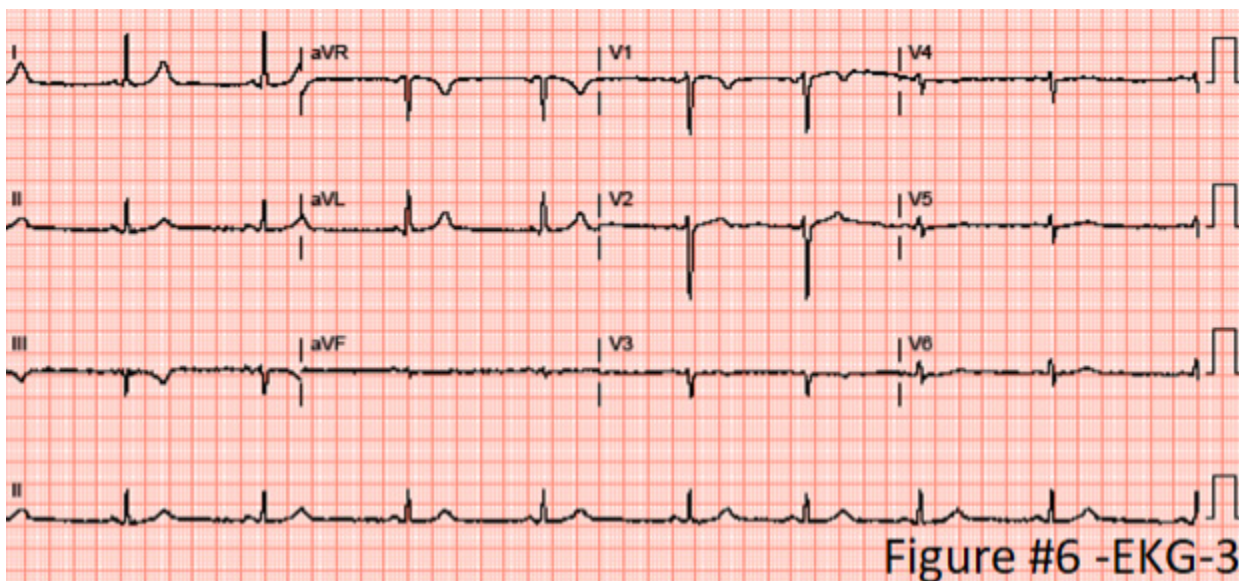
**FIGURE 3** Cardiac Catheterization- normal, no occlusion



**FIGURE 4** Cardiac Catheterization- normal, no occlusion



**FIGURE 5** Pulmonary angiography, No Pulmonary Embolism visualized



**FIGURE 6** EKG 3, pre-discharge

Rodriguez et al discussed potential pathogenic pathway by which iodinated contrast mediums cause immediate allergic reactions and delayed reactions.<sup>6</sup>

Gadolinium-based contrast mediums (GCMs) are used for magnetic resonance investigation. The incidence of hypersensitivity reaction to GCM has been reported to vary between 0.7% to 2.4% while severe anaphylactic reaction occurs 0.004 to 0.01% of patients.<sup>11,12</sup> There are various types of GCMs that are commonly utilized during magnetic resonance studies. For our patient gadobenate dimeglumine was being used for an MRI of the brain; it is a linear agent which is approved by FDA for central nervous

system MRIs.<sup>13</sup> The most common side effects listed by FDA are nephrogenic systemic fibrosis along with acute kidney injury and hypersensitivity. Cardiac arrhythmia is also listed as a side effect due to QTc prolongation but is not considered to be a major side effect.<sup>13</sup> A post-marketing surveillance study demonstrated that acute adverse reaction rate for gadobenate dimeglumine ranged from 0.024% to 15%.<sup>14</sup> The potential mechanism by which gadolinium causes hypersensitivity is not completely understood, but sensitization to gadolinium due to previous exposure is considered to be the most probable cause.<sup>7,12,15,16</sup>

As per reviewed literature, our patient had



an increased risk of gadolinium induced hypersensitivity. Studies have reported that gadolinium induced hypersensitivity is more common in women.<sup>7,17</sup> Gadolinium is primarily excreted through the kidney<sup>15</sup> and patients with elevated creatinine have a preponderance to hypersensitivity reactions. Our patient had a history of renal cell carcinoma, with an elevated creatinine of 1.4 and GFR of 44. Lastly, our patient had a remote history of an MRI with GCMs which probably would have worked as the sensitizing exposure. A case report by Singer et al similarly reported previous MRIs and exposure to gadolinium.<sup>15</sup>

The mechanism by which ACS occurs in concurrence with allergic reaction was explained by Dr. Kounis.<sup>5</sup> An allergic reaction is initiated when an allergen binds to the receptor bound IgE on mast cells or basophils and degranulation of inflammatory mediators occurs. These mediators are namely: histamine, chemokines, protease chymase, tryptase, cathepsin-D, proteoglycans, cytokines, peptides, growth factors, leukotrienes, thromboxane, platelet aggregating factor, prostacyclin and tumor necrosis factors.

The management of KS is challenging because of the coexistence of two conditions that have high fatalities. The treatment must be directed towards restoring circulation to the myocardium and abating the anaphylaxis. Corticosteroids have an integral part in countering the effects of anaphylaxis and despite their controversial use in ACS patients, they are deemed to be appropriate treatment for KS. Another group of medications that are considered to be efficacious are antihistamines; the use of both H1 and H2 antagonists such as diphenhydramine (1 to 2mg/kg) and ranitidine (1mg/kg) are advised, but the provider should keep in mind that concomitant use of these agents at a high rate causes hypotension leading to compromise of the coronary circulation, hence they should be infused slowly. Lastly, epinephrine can be used as it alleviates the life-threatening symptoms of anaphylaxis. Its use in KS is questionable as it has the potential to aggravate coronary vasospasm thereby potentiating the ischemia if administered intravenously. Hence, intramuscular dose of 0.2 to 0.5mg should be given every 5 to 15 minutes.<sup>18</sup>

Treatment of ACS should be provided in accordance to the American College of Cardiology Foundation guidelines. The preferred mode for reperfusion of the myocardium is percutaneous coronary intervention. Medical management entails use of aspirin and an additive antiplatelet such as clopidogrel, prasugrel or any P2Y12 inhibitors only if there is no contraindication. Symptomatic relief and resolution of vasospasm can be achieved by intravenous nitroglycerin and/ or calcium channel blockers.<sup>18,19</sup>

## CONCLUSION

Gadolinium-based contrast medium is generally a benign agent but in very rare cases it can lead to life threatening conditions and physicians should be aware of the detrimental side effects of this contrast medium and also should be aware of Kounis syndrome as a potential serious complication of the GCM.

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