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CASE REPORT

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Ondansetron-induced pseudoallergy with non-ischemic myocardial injury: A rare case report of Kounis syndrome

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Abstract

Ondansetron is an FDA-approved selective serotonin 5-HT3 receptor commonly indicated as an anti-emetic agent for nausea and vomiting. It is rare to observe fatal reactions from ondansetron despite having no allergies or previous exposure. We report a case of anaphylactoid reaction with spontaneous coronary vasospasms in response to intravenous ondansetron.

KEYWORDS

anaphylactoid reaction, immunology, Kounis syndrome, ondansetron, spontaneous coronary vasospasms

1 | INTRODUCTION

Ondansetron is an FDA-approved selective serotonin 5-hydroxytryptamine3 (5-HT3) receptor antagonist with several therapeutic applications and is commonly indicated as an anti-emetic agent for patients with severe nausea and vomiting.[1] Ondansetron has multiple mechanisms of actions by blocking serotonin on central sites and peripheral sites. Central antagonism targets the chemoreceptor trigger zone located on the fourth ventricle floor, while peripheral action affects the vagus nerve.[2,3] As a result, the trigger zone and the vagus nerve play a crucial role in the regulation of serotonin and are responsible for triggering nausea and emesis originating from the stomach.[4,5] Typically, ondansetron is indicated in patients with a history of chemotherapy, radiotherapy, drug poisoning, antidepressant therapies, head trauma, or gastrointestinal motility disorders that lead to symptoms of emesis.[6] A meta-analysis by Piechotta et al.[6] revealed that ondansetron alone or in combination with other antiemetic agents effectively controlled the vomiting due to chemotherapy in adults. However, recent studies have also shown the efficacy of ondansetron in reducing the number of vomiting episodes in pediatric patients with acute gastroenteritis.[7,8]

The majority of 5-HT3 receptor antagonists have been associated with electrocardiogram changes that are insidious and asymptomatic in onset.[9] Common side effects of ondansetron include headaches, dizziness and diarrhea, or constipation.[10] However, it is a rare entity to observe potentially fatal reactions such as coronary vasospasms and

Eden Firew and Helen Huang shared joint first-authorship.

hypersensitivity skin reactions from ondansetron despite having no allergies to the drug. In this report, we present a rare case of an anaphylactoid reaction with spontaneous coronary vasospasms in response to intravenous ondansetron.

2 | CASE HISTORY/EXAMINATION

A 45-year-old man presented to the emergency department with four episodes of vomiting of ingested food. It is non bilious, non-projectile and does not contain blood. He has periumbilical non-radiating abdominal pain with gradual onset of 3 days duration. He was previously diagnosed with mild duodenitis via endoscopy, for which he had initiated treatment with oral Esomeprazole 40 mg per day for a month. The patient's medical history was otherwise not noteworthy. His family history was noncontributory. He occasionally drinks 2 units of alcohol but has no history of drug use or smoking.

On admission, he had a body temperature 36.4°C, a blood pressure of 120/80 mmHg, a respiratory rate of 16 breaths/min, a heart rate of 72 beats/min, and an oxygen saturation of 95% of room air. On physical examination, we noticed the patient had dry mucosa and mild epigastric tenderness. His cardiovascular and respiratory examinations were normal. Results of his abdominal examination was normal, and he had no lower-extremity edema. A summary of his laboratory investigations is reported in Table 1. A baseline ECG was obtained, which showed a normal sinus rhythm with non-ischemic changes (Figure 1). His cardiac troponin T levels was initially 2.8 ng/dl.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, INVESTIGATIONS AND TREATMENT

He was diagnosed with acute exacerbation of dyspepsia and treated with a single 8 mg dose of ondansetron intravenously. Within a few seconds after taking around 0.5 ml (2 mg) of ondansetron, the patient developed chest tightness, redness, and burning sensation around the injection site along with urticaria, hypotension and bronchospasm. He was immediately treated with hydrocortisone 100 mg intravenously, and the reaction resolved within a few minutes. His vital signs were as follows: body temperature, 36.2°C; blood pressure, 90/60 mmHg; respiratory rate, 20 breaths/min; heart rate, 94 beats/min; and oxygen saturation, 88% on room air.

TABLE 1 A summary of laboratory values obtained from the patient in comparison with the normal values reported by the American College of Physicians[11]

Investigations	Report	Reference values
White blood cell count/mm^3	7040	4000–10,000
Hemoglobin (g/dl)	15.8	14–17
Hematocrit (%)	47.4	41–51
Platelet count/mm^3	196,000	150,000–350,000
Serum sodium (mmol/L)	140	136–145
Serum potassium (mmol/L)	4.2	3.5–5.0
Serum calcium (mg/dl)	10.2	9–10.5
Aspartate aminotransferase (U/L)	28	0–35
Alanine aminotransferase (U/L)	65	0–35
Serum creatinine (mg/dl)	0.9	0.7–1.3
Serum urea (mg/dl)	22	8–20
Cardiac troponin T (ng/dl)	2.8	0–0.10

An ECG was obtained 15 min after administration of ondansetron which showed no change from the baseline ECG. However, the patient's cardiac troponin T levels had elevated to 812 ng/L, a 42× increase from his previous levels. The patient was followed up 15 min later following the reaction, where he complained of severe headache, dizziness, and fatigue. It was noted that the other symptoms had subsided. He was given once-off aspirin loading dose of 312 mg orally. A subsequent ECG and cardiac troponin was repeated every 6 h and showed normal ECG and serial drop in troponin levels of 231, 178, 128, and 78 ng/L.

4 | OUTCOME AND FOLLOW-UP

On follow-up of his previous reaction, we inquired about his previous usage of ondansetron and reported no history of drug or food allergies and no previous exposure to ondansetron. Additionally, he does not have a history of surgery or chemotherapy. He was then referred to the cardiac center for complete cardiac evaluation. An echocardiogram demonstrated mild left ventricular hypertrophy with normal ejection fraction with no ischemic changes. He also underwent a cardiac stress test and had no chest pain or ECG changes. There was no indication for cardiac catheterization and the patient was discharged. It was concluded that the sudden cardiac event was most likely ondansetron-induced coronary spasm that resolved spontaneously. Based on the allergic reaction that ensued prior to these presentations, Kounis syndrome was suspected as a probable cause.

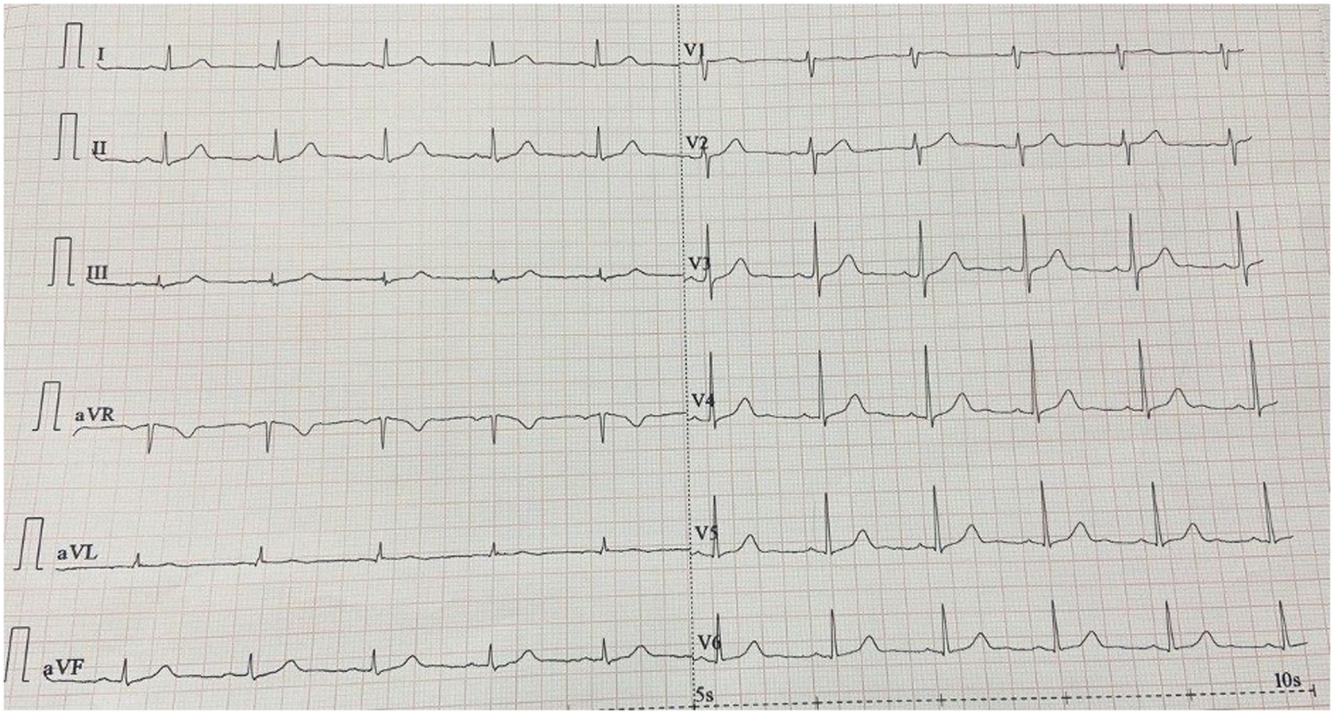

FIGURE 1 Normal ECG with no ischemic changes.

5 | DISCUSSION

Ondansetron is considered as a first-line agent in the ED to manage nausea and vomiting, with a relatively low risk of side effects compared with other antiemetics.[12,13] Despite the high safety profile of ondansetron, emerging literature on ondansetron toxicity has reported hypersensitivity reactions leading to skin rashes and urticaria.[14] It is entirely possible that with a combination of bronchospasms, hypotension, and urticaria-like rash at the site of injection, this patient had an allergic reaction to ondansetron prompting hydrocortisone administration. Allergic reactions to drug administration can be classified into two categories: Anaphylaxis (IgE-immune mediated) or Anaphylactoid reactions (non-IgE-immune mediated).[15] Anaphylaxis is often caused by a hypersensitivity reaction to drugs in hospital settings.[16] Pre-sensitized individuals exposed to an allergen prompt an immunological response involving IgE antibodies initially binding to mast cells and basophils, and later cross-linking with other IgE antibodies to initiate the signal transduction cascade of preformed mediators.[17] On the other hand, anaphylactoid reaction is independent of antigen-specific immune responses and mimics symptoms of anaphylaxis (Figure 2). Also known as a pseudo allergy, this phenomenon often occurs from the first dose of medication and can attribute to around two-thirds of hypersensitivity reactions.[18] Typically, they are induced by opioid (i.e., codeine), complement activation-related drugs, non-steroidal anti-inflammatory drugs (i.e., aspirin), or traditional Chinese medicine injections.[19] However, pseudo allergies are well underreported in the literature and can come with lethal complications due to its unpredictability. Though IgE levels were not determined, the absence of prior exposure to ondansetron nor any history of adverse allergic reaction to drugs makes it likely that this patient experienced an anaphylactoid reaction to ondansetron. Mehra et al.[14] reported a similar case of hypersensitivity to intravenous ondansetron which was concluded to be an anaphylactoid reaction due to the absence of prior administration in the patient's history.

Acute coronary syndrome was first reported in 1992 as an adverse effect of ondansetron.[20] Since then, there have been nine documented cases of coronary vasospasms and dysrhythmia after ondansetron administration to date.[21] When the occurrence of cardiac symptoms arise in the context of anaphylactoid reactions to drugs, the condition can be coined as "Kounis Syndrome (KS)." Despite KS being underreported, its pathophysiology is well discerned and can be attributed by an immune response generated from an anaphylactoid reaction, causing myocardial injury. Mast cell activation caused by an allergic reaction to a drug can cause the release of interrelated inflammatory cells such as T lymphocytes through mast cell activation[22] (Figure 2). The heart is a target of these chemical mediators during anaphylactoid reactions and can cause localized effects on the myocardium, leading to acute myocardial injury (non-ischemic changes), ACS such as myocardial infarctions, and vasoconstriction of

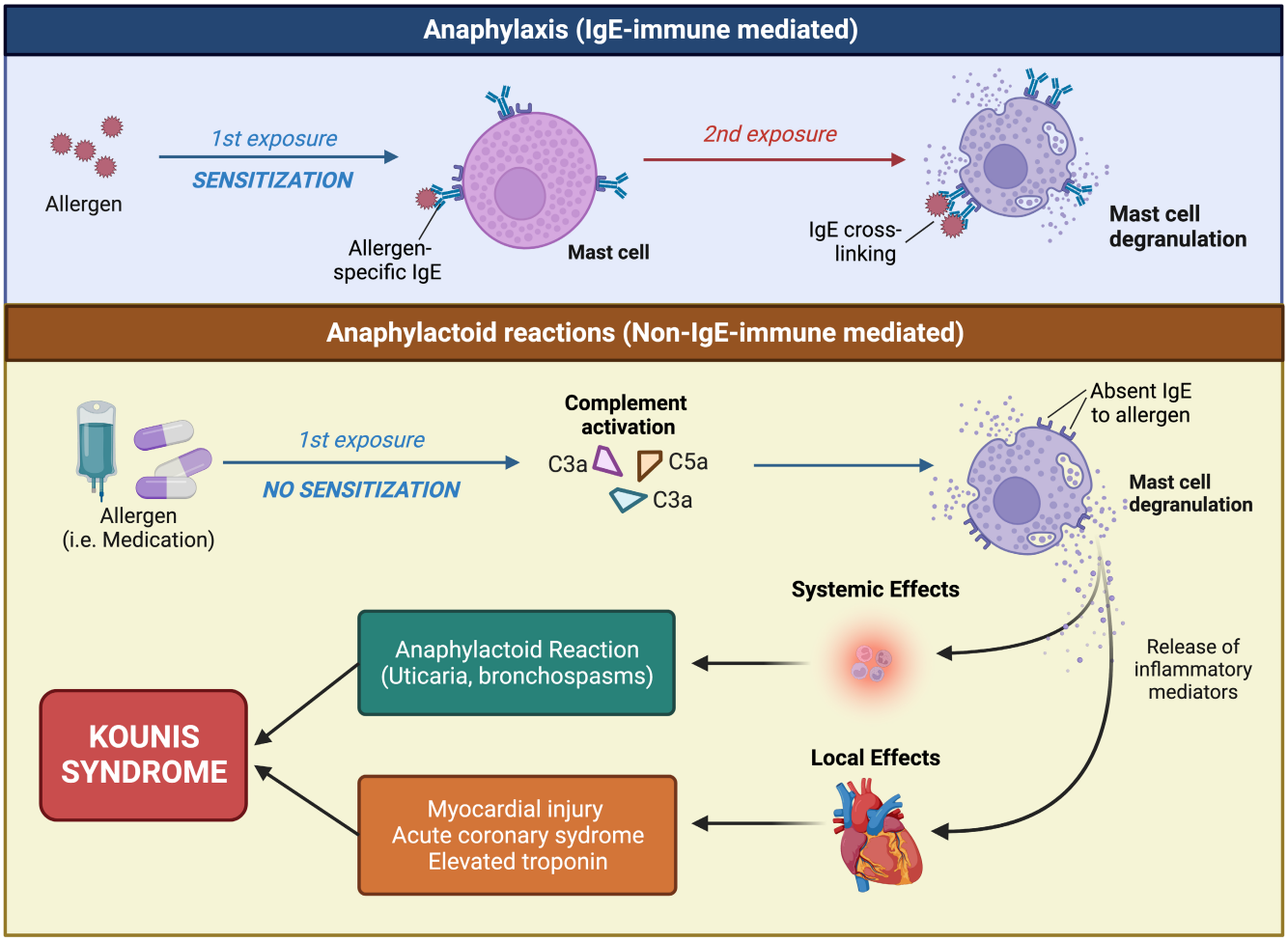

FIGURE 2 Pathophysiology of Kounis Syndrome characterized by non-ischemic myocardial injury and elevated troponin due to an anaphylactoid (non-IgE-immune-mediated) reaction to ondansetron (Original image created with Biorender.com by HH).

coronary vasculature.[22] The investigations that would support KS include troponin levels, ECG, and ECHO. The only other case study reporting KS after ondansetron administration described pregnant women experiencing a possible allergic reaction to ondansetron, leading to acute coronary syndrome. In the aforementioned case, a coronary angiography was indicated in to confirm the hypothesis of a coronary vasospasm and an ECG exhibited ST-segment elevations.[23] In our study, though there was an absence of ischemic changes and non-abnormal ECG changes, there were very high elevations of cardiac troponin levels. In a previously reported clinical study, 31 patients with anaphylaxis and urticaria was found with significantly increased cardiac troponin I levels compared to healthy controls.[24] This was further confirmed by Cha et al.,[25] where myocardial injury and elevated troponin levels was observed in 300 anaphylaxis cases. Given the patient's medical history, an angiography was not ordered since his symptoms subsided after immediate administration of aspirin. On the echocardiogram, left ventricular hypertrophy was noted, an occurrence that has been reported once in a case series on KS by Forlani et al.[26] Due to the variety of cardiac manifestations and presentations, it can be difficult to interpret the exact pathophysiology. However, it is reasonable to suggest that the non-ischemic nature of the patient's cardiac symptoms were attributed by the acute nature of injury inflicted by anaphylactoid reactions, causing a rise in troponin and leading to hypertrophy as compensation. In accordance with the results of previous investigations, cardiac troponin levels may serve as an important marker in patients with acute allergic reactions.[25]

To our best knowledge, this was one of the first cases of KS characterized by non-ischemic myocardial injury and elevated troponin due to an anaphylactoid reaction to ondansetron. As a result, we bring awareness to the multi-faceted nature of KS and the importance of taking detailed history. If left untreated or misdiagnosed, the consequences can be detrimental to the patient's health.[22] A high index of clinical suspicion must be exercised when a patient is suspected to have a combination of allergic reactions and cardiac symptoms. However, the timing

of hypersensitivity symptoms superimposed with non-ischemic cardiac changes in our case made it difficult to diagnose KS. Future studies are warranted to further study how anaphylactoid reactions play a role in non-ischemic changes as opposed to ACS and whether the time of presentation is important in the diagnosis. Moreover, further investigations should ascertain the association of pseudo allergies or anaphylactoid reactions with an increase in cardiac troponin levels. This case prompts a need to better distinguish anaphylactoid reaction from anaphylaxis when administering ondansetron and brings to light the multi-factorial presentation of Kounis syndrome.

There were several limitations to the case report. We did not obtain an angiogram, which would definitively diagnose a spontaneous coronary vasospasm that ensued after ondansetron administration. However, the results from the investigations raised our suspicions of spontaneous and acute myocardial injury that could have been caused by vasospasms given the lack of previous cardiovascular co-morbidities. Additionally, we did not determine the IgE levels of the patient, which would have strengthened our confidence that the patient has a pseudo allergy to ondansetron.

6 | CONCLUSION

Ondansetron, an anti-emetic with a relatively high safety profile, is prescribed globally for the symptom of vomiting. This was one of the first cases of KS characterized by non-ischemic myocardial injury and elevated troponin due to an anaphylactoid reaction to ondansetron. KS have potential effects on biochemical parameters such as cardiac troponin along with an anaphylactoid phenomenon after an intravenous administration of the recommended dose. Thus, this case warrants more research for establishing the pathophysiology of KS, the association of cardiac troponin with anaphylactoid reactions, and ensure the judicial use of ondansetron.

AUTHOR CONTRIBUTIONS

Eden Firew: Conceptualization; data curation; investigation; project administration; resources; supervision; validation; visualization; writing – original draft; writing – review and editing. **Helen Huang:** Conceptualization; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing. **Ayush Anand:** Formal analysis; investigation; methodology; project administration; supervision; validation; writing – original draft; writing – review and editing. **Yonathan Aliye Asfaw:** Conceptualization; data curation; methodology; project administration; resources; supervision; writing – review and editing. **Charmy Parikh:** Formal analysis; investigation; methodology; validation; visualization; writing – original draft; writing – review and editing. **Humza Rafique Khan:** Formal analysis; investigation; methodology; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST

The authors do not have any relevant conflict of interests to disclose.

DATA AVAILABILITY STATEMENT

This manuscript has all the data relevant to this case report included.

ETHICAL APPROVAL

Ethical approval was not required.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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