JACC: CASE REPORTS VOL. 3, NO. 14, 2021

CASE REPORT

ADVANCED

CLINICAL CASE

Kounis Syndrome Associated With Takotsubo Syndrome in an Adolescent With Peutz-Jeghers Syndrome

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ABSTRACT

We describe the case of a 15-year-old female patient with Peutz-Jeghers syndrome who presented with vomiting and abdominal pain secondary to ileoileal invagination. Initial analgesic treatment was not effective, and subsequent tramadol infusion resulted in clinical manifestations compatible with Kounis and Takotsubo syndromes. However, the patient had an excellent recovery. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1602–1606)

HISTORY OF PRESENTATION

A 15-year-old female patient with Peutz-Jeghers syndrome was admitted to the emergency department of another hospital because of vomiting and abdominal pain. Alizapride and paracetamol, followed by ketorolac, were administered. Vital signs were within limits, and she was afebrile. An abdominal ultrasound scan revealed ileoileal invagination. Because of persisting abdominal pain, a tramadol infusion was started. During the tramadol infusion, the patient had a reaction characterized by generalized skin rash. Moreover, high blood pressure (blood pressure, 140/105 mm Hg) was recorded, and headache developed. A few minutes later, orthopnea and dyspnea occurred in association with widespread pulmonary rales, suggestive of acute pulmonary edema. Heart sound auscultation showed a systolic murmur grade 2/6 on the Levine scale. After 2 hours, the patient's blood pressure dropped to 80/50 mm Hg, her peripheral blood oxygen saturation level was 89% without oxygen support, heart rate was 100 beats/min, respiratory rate was 30 breaths/min, body temperature was 36.2 °C, and Glasgow Coma Scale score was 15.

LEARNING OBJECTIVES

- To be able to make a differential diagnosis among common causes of acute heart failure in pediatric patients.
- To be aware of the potential cardiac complications of "pharmacological cocktails" and hypersensitivity reaction.
- To consider that KS and TTS may coexist in the same patient.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 9, 2021; revised manuscript received July 7, 2021, accepted July 13, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.07.008

The patient was transferred to our center (Meyer Children's University Hospital, Florence, Italy), which is the regional pediatric referral center. The electrocardiogram (ECG) showed ST-segment elevation in leads I and aVL, as well as ST-segment depression in the inferior leads (**Figure 1A**). The echocardiogram showed severe left ventricular (LV) dysfunction (ejection fraction [EF], 25%) (Video 1) resulting from diffuse middle and basal hypokinesia and moderate mitral regurgitation. During the echocardiographic evaluation, a normal origin of both coronary arteries was documented; the left anterior descending (LAD) coronary artery had a uniform diameter of 3.2 mm, without the typical taper, and it was surrounded by hyperechoic tissue (**Figure 2**). Chest radiography revealed bilateral hilar congestion and diffuse lung consolidations. Laboratory tests revealed a progressive increase of high-sensitivity troponin T (hs-cTnT) (up to 820 pg/mL) and of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (up to 22,000 pg/mL) in 24 hours (**Figure 3**). Total blood count showed leukocytosis (23,600/μL), and procalcitonin, C-reactive protein, and lactate were mildly increased (0.8 ng/mL, 2.15 mg/dL, and 2.3 mmol/L, respectively). The patient was then transferred to the intensive care unit.

On admission, another ECG was recorded, showing sinus tachycardia, Q waves in leads I and aVL, poor R-wave progression in leads V_1 to V_4, and ST-segment elevation, with inverted T waves in the same leads and nearly complete resolution of the ST-segment elevation (**Figure 1B**). Acute pulmonary edema developed. An abdominal computed tomography scan confirmed the intestinal invagination leading to a life-threatening situation. Emergency surgical intervention was considered mandatory. Thus, peripheral cannulas for venoarterial extracorporeal membrane oxygenation were placed in the event of the potential need for circulatory support. The patient was transferred to the operating room, and she underwent a 40-cm ileal resection.

The postoperative course was uneventful and was characterized by hemodynamic improvement leading, after 3 days, to gradual inotropic treatment interruption. Serial echocardiograms showed progressive LV function recovery up to 48% of EF

ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

EF = ejection fraction

hs-cTnT = high-sensitivity cardiac troponin

KS = Kounis syndrome

LAD = left anterior descending (coronary artery)

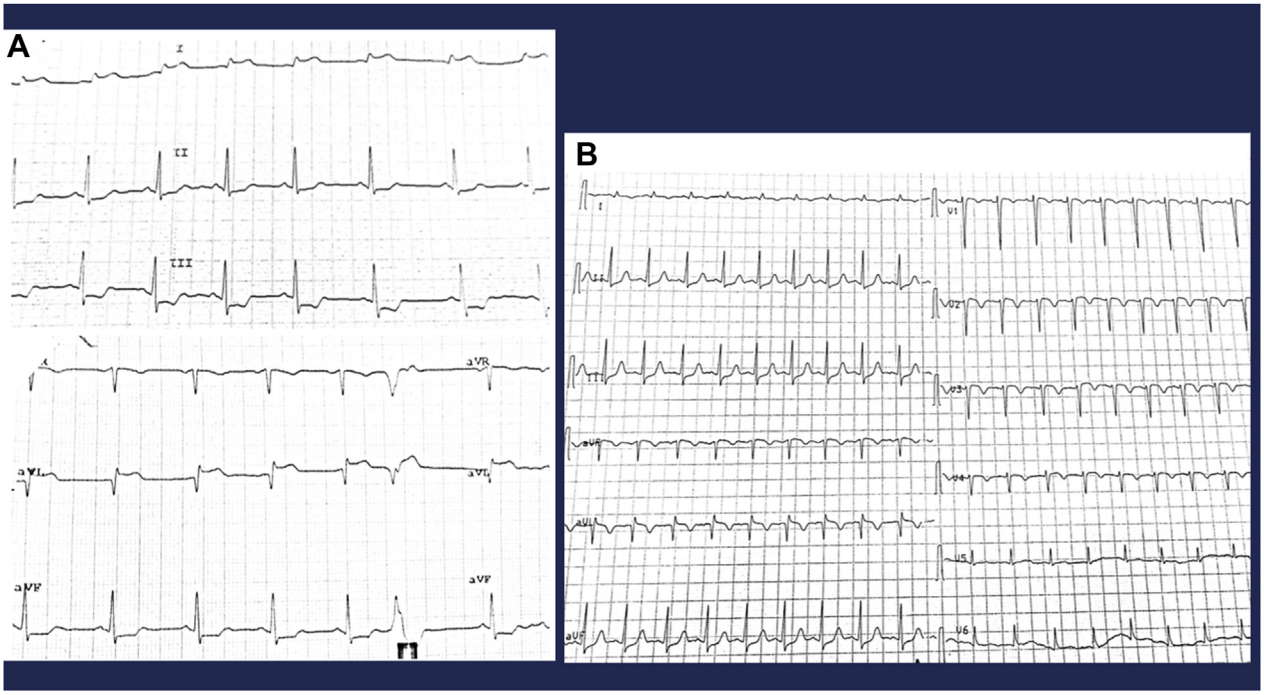
LV = left ventricular

NT-proBNP = N-terminal pro-B-type natriuretic peptide

sIgE = specific immunoglobulin E

TTS = Takotsubo syndrome

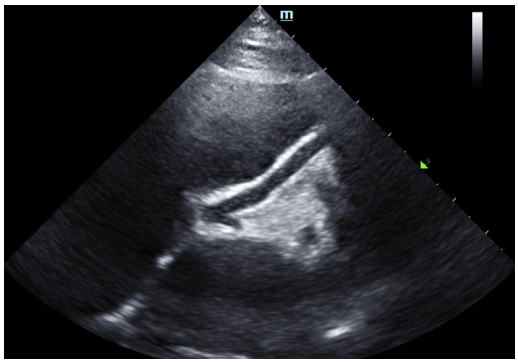
FIGURE 1 Electrocardiographic Findings



(A) Electrocardiogram on admission showing ST-segment elevation in leads I and AVL as well as ST-segment depression in the inferior leads. **(B)** Electrocardiogram recorded in the intensive care unit showing sinus tachycardia, Q waves in leads I and aVL, poor R-wave progression in leads V_1 to V_4 and ST-segment elevation with inverted T waves in the same leads.

JACC: CASE REPORTS, VOL. 3, NO. 14, 2021
OCTOBER 20, 2021:1602–1606

FIGURE 2 Echocardiographic Evaluation of the Left Anterior Descending Coronary Artery Surrounded by Hyperechoic Tissue



(residual septal hypokinesis) after 6 days, and the LAD artery diameter was normal.

A week after the admission, the patient's clinical condition significantly improved. She remained afebrile, without signs or symptoms, and hemodynamically stable. Her blood hs-cTnT and NT-proBNP values progressively decreased (**Figure 3**), as did her procalcitonin, C-reactive protein, and lactate values. Chest radiography showed resolution of the lung congestion. The electrocardiographic abnormalities resolved. On day 11, the patient underwent cardiac magnetic resonance with and without a gadolinium infusion; the imaging showed findings suggestive of edema with the absence of late gadolinium enhancement (**Figures 4A to 4D**).

PAST MEDICAL HISTORY

In the past medical history of this patient with Peutz-Jeghers syndrome, there were several intestinal polypectomies, as well as a recent hospitalization for ileoileal invagination that was treated conservatively. She had rhinoconjunctivitis from 10 years of age, with sensitization to inhalant allergens (dust mite, animal dander, and pollens). However, the girl did not have cardiovascular disease in her past clinical history or acute illnesses in the previous month. Furthermore, the familiar history was negative for cardiovascular disease or sudden death, although it was positive for atopic diseases (mother with rhinoconjunctivitis and asthma, with sensitization to inhalant allergen).

DIFFERENTIAL DIAGNOSIS

Takotsubo syndrome (TTS), myocarditis, serotonin syndrome, and Kounis syndrome (KS) were considered. The ECG abnormalities, the transient LV dysfunction with diffuse middle and basal hypokinesia, the BNP elevation, and a potential physical trigger (invagination) first suggested the diagnosis of TTS. However, headache and hypertension within a likely time frame with potentially associated drugs (tramadol and alizapride) suggested possible serotonin syndrome, but that was ruled out on the basis of the diagnostic criteria (1).

The results of cardiac magnetic resonance with and without a gadolinium infusion let us exclude myocarditis. This decision was also supported by the clinical course of the patient.

Conversely, the close temporal association between the drug treatment and the clinical manifestations (probable association according to the Naranjo scale), including a skin rash and the onset of transient heart failure with diffuse middle and basal hypokinesia, raised our suspicion of KS. Moreover, electrocardiographic and echocardiographic findings additionally supported this hypothesis, and tramadol has already been described as a potential trigger for KS (2).

INVESTIGATIONS

The patient underwent skin prick testing with tramadol (50 mg/mL), with a negative result. According to current standards, histamine, 10 mg/mL (Lofarma), and normal saline were used as positive and negative control substances, respectively. Furthermore, research into serum-specific immunoglobulin E (sIgE) against tramadol was performed by using radioimmunoassay with the solid phase obtained by coupling the tramadol to epoxy-activated sepharose (Sepharose 6B, Cytiva Life Sciences), and the result was negative (radioactive uptake, 0.69%; nonspecific binding, 0.53%; values >3 times the nonspecific binding are considered positive).

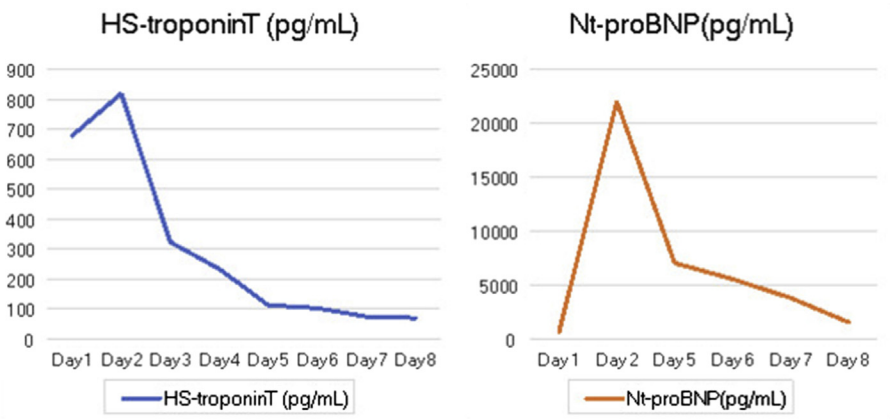
MANAGEMENT

In the acute phase, pulmonary edema was treated with a furosemide infusion and continuous positive airway pressure support, with rapid clinical and radiologic improvement. The patient's hemodynamic instability required the administration of levosimendan and epinephrine. After partial recovery, treatment with a low dose of bisoprolol was introduced because of residual systolic dysfunction, and the patient was discharged on therapy with this drug.

DISCUSSION

KS is a coronary hypersensitivity disorder characterized by an anaphylactoid, anaphylactic, allergic, or

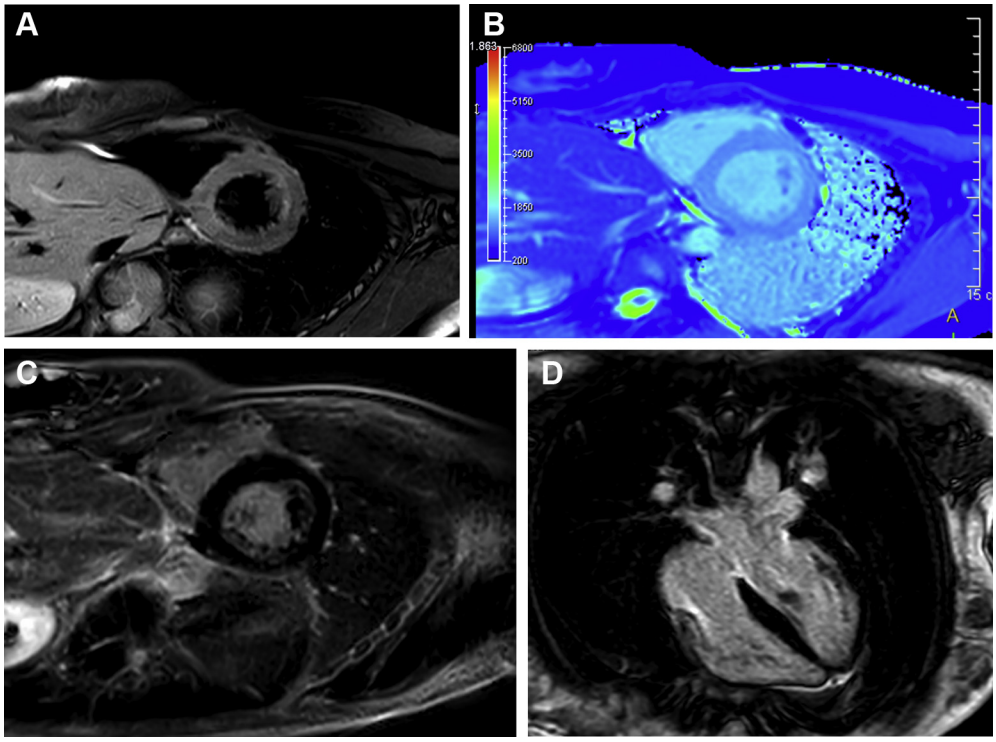
FIGURE 3 High-Sensitivity Troponin T and N-Terminal Pro-B-Type Natriuretic Peptide



HS = high sensitivity; Nt-proBNP = N-terminal pro-B-type natriuretic peptide.

hypersensitivity reaction associated with an acute coronary syndrome (3). Possible causes of KS include several substances, such as tramadol in our patient, and environmental exposures. Mast cells are well represented in the cardiac tissues, by locating preferentially inside the coronary arteries, where they can degranulate. Thus, we suppose that the echocardiographic finding of transient LAD artery dilatation

FIGURE 4 Cardiac Magnetic Resonance Findings



(A) T_2-weighted sequence showing a hyperintense signal in the interventricular septum and the posterior and anterior wall of the left ventricle, findings suggestive of edema. **(B)** T_1 mapping sequence suggestive of diffuse edema. **(C and D)** Absence of late gadolinium enhancement.

surrounded by hyperechoic tissue that could represent inflammatory infiltration and edema (**Figure 2**) additionally supported the KS hypothesis in our case. To the best of our knowledge, we report such a potential characteristic for the first time.

Although it is rare, KS can occur in pediatric patients, and it should be suspected, for example, in patients with chest pain developing in the context of a potential reaction, associated with ST-segment abnormalities and transient wall motion dysfunction (4). A possible role of cardiac magnetic resonance in KS has been suggested, to identify an early-phase subendocardial contrast defect and edema without late gadolinium enhancement as typical features (5).

An increase of tryptase and the demonstration of a specific allergic sensitization against the potential trigger of the reaction could support the diagnosis of KS. Unfortunately, serum tryptase was not analyzed in our patient, and it was not possible to identify a specific sensitization through skin testing or sIgE. However, these negative results cannot rule out KS (6). Indeed, the patient was advised to strictly avoid drugs potentially associated with the event in the future.

Conversely, TTS is a transient form of LV dysfunction that mimics an acute coronary syndrome, usually triggered by an emotional or physical stressor (7). Most commonly described in postmenopausal women, TTS has also been reported in patients younger than 18 years of age (8). Compared with adults, who usually present chest pain, pediatric patients more commonly have heart failure, usually with more severe LV impairment and nonapical variants. Cardiac magnetic resonance is required for the diagnosis, especially in patients with nonapical TTS; a typical finding in TTS is myocardial edema without late gadolinium enhancement (9).

FOLLOW-UP

At 1-month and 1-year follow-up, the clinical manifestations were absent, and the patient showed normal electrocardiographic and echocardiographic findings (Video 2).

CONCLUSIONS

According to the clinical data collected, our patient had KS associated with TTS. Indeed, as already demonstrated in published reports, both TTS and KS can coexist in the same patient (10). However, the adolescent in our case had a favorable outcome.

ACKNOWLEDGMENTS The authors thank Dr Ioanna Koniari (University Hospital of South Manchester NHS Foundation Trust, Manchester, United Kingdom) for critical review of the manuscript. Written informed consent was obtained from the minor's legal guardian for the publication of any potentially identifiable data included in this article.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS acute heart failure, cardiac magnetic resonance, echocardiography, inotropic agents, myocardial ischemia, pulmonary edema

APPENDIX For supplemental videos, please see the online version of this paper.