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CASE REPORT

Allergic Angina with QTc Prolongation and Wellens Type-A Syndrome Post-ceftriaxone Parallel to COVID-pneumonia-A New Causation and Treatment

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ABSTRACT

Rationale: Antibiotics may cause serious adverse effects. Allergic acute coronary syndrome (ACS) or Kounis Zafras (KZ) syndrome is a newly described syndrome relevant to allergen exposure. Coronavirus disease 2019 (COVID-19) infection may have lethal cardiovascular and respiratory complications. Wellens syndrome is particular for critical stenosis of the left anterior descending artery. However, there is a strong relationship between coronary artery disease and COVID-19 infection. **Patient Concerns:** A 28-year-old married homemaker Egyptian female patient was admitted to the intensive care unit with angina, QTc prolongation, and Wellens type-A syndrome after ceftriaxone injection post-COVID-pneumonia. **Diagnosis:** Allergic angina with QTc prolongation and Wellens type-A syndrome post-ceftriaxone Parallel to COVID-pneumonia. **Interventions:** Oxygenation, arterial blood gas, electrocardiography, and echocardiography. **Outcomes:** Gradual dramatic clinical, and electrocardiographic improvement had occurred. **Lessons:** Ceftriaxone-inducing allergic ACS or KZ syndrome with QTc prolongation and Wellens type-A syndrome post-COVID-pneumonia is a distinctive new adverse effect. The widespread non-ST-segment elevation myocardial infarction with ST-segment elevation in aVR lead and T-wave inversion in anterolateral leads or Wellens syndrome type A may be interpreted as accompanied by multi-vessels disease. An associated COVID-19 infection may be an exacerbated factor for the ceftriaxone-inducing allergic ACS.

Keywords: Allergic coronary syndrome, ceftriaxone, coronary artery disease, coronavirus, coronavirus disease 2019, Kounis Zafras syndrome, long QT syndrome, pneumonia, QT/QTc interval

INTRODUCTION

Allergic acute coronary syndrome (ACS) or Kounis Zafras (KZ) syndrome is hallmarked as the co-association of an ACS with hypersensitivity reactions following an allergenic exposure.[1] KS was initially identified by Kounis and Zavras in 1991 as an "allergic angina syndrome", "allergic angina" or "allergic myocardial infarction".[1,2] There is ACS-associated mast cell activation from allergic, hypersensitivity, or anaphylactoid reactions.[2] The essential pathogenesis of KS is the inflammatory cytokines mediators released through mast cell activation during a hypersensitivity reaction triggered by food, insect bites, or drugs. There is a subsequent coronary artery spasm (CAS) with possible atheromatous plaque erosion or rupture.[2] The allergic angina commonly starts within 1 h of exposure to the offending allergen. Longer onset ACS also have been reported.[3] Variant presentations of KS have been reported.[2] Three different variants of KS have been described: Type I occurs in structurally normal coronary arteries with no cardiovascular risk factors. The coronary spasm was suggested. With or with no associated acute myocardial infarction (AMI). Type II KS occurs in patients with pre-existing ischemic heart disease, in whom the acute release

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of inflammatory mediators induces CAS that may lead to plaque rupture and myocardial infarction. Type III KS occurs in patients with coronary artery stent-associated thrombosis.[1,3-5] Ceftriaxone is a third-generation semisynthetic cephalosporin that has a long half-life.[6] It was approved for use in the US in 1984.[7] It is administered intravenously or intramuscularly and has a broad spectrum of activity against Gram-positive and Gram-negative aerobic, and some anaerobic, bacteria. Ceftriaxone has generally been well tolerated by adults and children following intravenous (IV) and intramuscular injection. The commonest adverse effects were diarrhea, rash, and reactions at the injection site such as phlebitis and pain on intramuscular injection.[6] Ceftriaxone's adverse effects are usually well-tolerated. It includes diarrhea, nausea, abdominal pain, dyspepsia, headache, rash, and rarely; clostridium difficile-associated diarrhea, hypersensitivity, angioedema, anaphylaxis, and Stevens–Johnson syndrome/toxic epidermal necrolysis.[7] The QT-interval is an electrocardiography (ECG) phase measured in milliseconds (ms) from the beginning of the QRS complex until the end of the T-wave. It represents the ventricular depolarization followed by the ventricular repolarization. It is used as a hallmark for a prolongation of the ventricular repolarization time. A prolonged QTc-interval is considered if higher than 450 ms in adult males and higher than 470 ms in adult females.[8] QT prolongation is an imperfect biomarker for proarrhythmic risk.[9] A prolonged QTc interval can lead to ventricular arrhythmias (torsades de pointes) and sudden cardiac death (SCD).[8] For the risk of SCD, "borderline QTc" in males is 431–450 ms; and, in females, 451–470 ms. An "abnormal" QTc in males is a QTc above 450 ms; and, in females, above 470 ms.[10] All patients with long QT syndrome (LQTS) should avoid drugs that prolong the QT interval or that reduce their serum potassium or magnesium levels.[11] Beta-blockers are the drugs of choice for patients with LQTS.[12,13] An inverted T-wave is described as a T-wave > 1 mm below the isoelectric line in two or more adjacent leads. However, a biphasic T-wave is defined as an inverted T-wave if the T-wave is > 1 mm below the isoelectric line in the terminal part of the T-wave.[14] There are two main causes of biphasic T waves: Myocardial ischemia and hypokalemia. The two waves go in opposite directions. Biphasic T-wave due to ischemia goes up and then down.[15] Wellens syndrome is a pattern of inverted or biphasic T-wave in V2-3 (in patients presenting with/following ischemic-sounding chest pain) that is highly specific for critical stenosis of the left anterior descending artery. There are two patterns of T-wave abnormality in Wellens syndrome: (1) Type A is a biphasic T-wave with the initial deflection positive and the terminal deflection negative (25% of cases). (2) Type B is a T-wave that is deeply and symmetrically inverted (75% of cases).[15] The systemic inflammatory response in severe coronavirus disease 2019 (COVID-19) is the output of raised levels of cytokines causing cytokine-release syndrome that can destroy multiple tissues, including vascular endothelium and cardiac myocytes. Plaque rupture AMI due to the systemic inflammation and catecholamine surge in this disease. Coronary thrombosis also has been recognized as a cause of AMI in COVID-19 patients.[16,17]

CASE PRESENTATION

A 28-year-old married homemaker Egyptian female patient was referred to the intensive care unit (ICU) with angina and palpitations. Dizziness, circumorally numbness, extremities paresthesia, fatigue, loss of appetite, loss of smell, and generalized body aches were associated symptoms. She gave a recent history of IV injection of 2 g ceftriaxone for a recent chest infection 2 h ago. She gave a history of fever 4 days ago. Currently, she has a history of contact with his relative who confirmed a COVID-19 patient in the past 11 days. Upon general physical examination; generally, the patient was tachypneic, and distressed, with a regular pulse rate (ventricular rate [VR] of 70), blood pressure of 120/70 mmHg, respiratory rate of 20 bpm, a temperature of 37.5°C, pulse oximeter of oxygen (O2) saturation of 95%, and Glasgow coma scale of 15/15. Tests for provocative latent tetany were positive. No more relevant clinical data were noted during the clinical examination.

The patient was admitted to ICU with ceftriaxone-inducing angina. Initially, the patient was treated with O_2 inhalation by O_2 inhalation central system (100%, by simple mask, 5L/min). The patient was maintained and treated with aspirin; 4 oral tablets (75 mg, then OD), clopidogrel; 4 oral tablets (75 mg, then OD), diltiazem tablets (60 mg, OD), enoxaparin SC (60 mg, BID), oral nitroglycerine capsule (2.5 mg, BID), and atorvastatin (20 mg, OD). Hydrocortisone sodium succinate (100 mg IV BID), azithromycin tablets (500 mg, OD), oseltamivir capsules (75 mg, BID only for 5 days), and paracetamol (500 mg IV every 8 h as needed) were added. The patient was hourly monitored for vital signs and O2 saturation. The initial ECG was done on the initial ECG on presentation in the point-of-care (POC) showing normal sinus rhythm (NSR) (VR of 72) with ST-segment depression in high lateral leads, anterolateral leads, and inferior leads. There is ST-segment elevation in aVR lead [Figure 1a]. The second ECG tracing was taken on the initial ECG on presentation within 30 min after ICU admission showing NSR with ST-segment depression in lead I, anterolateral leads, and inferior leads. There is ST-segment elevation in aVR lead [Figure 1b]. The initial complete blood count (CBC); hemoglobin was 11.7 g/dL, RBCs; 4.38 × 10^3/mm^3, white blood cells; 18.9 × 10^3/mm^3 (neutrophils; 88.4%, lymphocytes: 9.8%, monocytes; 1.1%, eosinophils; 0.7% and basophils 0%), platelets; 481 × 10^3/mm^3. arterial blood gas was (PH; 7.469 mmHg, PCO_2; 23.4 mmHg, HCO_3; 16.6 mmHg, SO_2; 99.4%, and PaO_2; 217.2 mmHg). C-reactive protein was (12 mg/L). Serum glutamic-pyruvic transaminase was (57 U/L) and serum glutamic-oxaloacetic transaminase was (30 U/L). Serum albumen was (4.8 mg/dL). Serum creatinine was (0.7 mg/dL). Random blood sugar was (127 mg/dL). Total calcium was (8.11 mg/d). Ionized calcium was (3.81 mg/d). The troponin I test was (9.62 U/L). The Creatine Kinase-MB was (37 U/L). Echocardiography was done on the 4th day of the presentation showing a mild thickened tip of anterior mitral valve leaflet prolapse and mild mitral regurgitation with an eccentric jet of an ejection fraction of 62% [Figure 2]. Serial ECG tracings were done. The third ECG tracing was taken within 7 h of the ICU management showing NSR (VR of 74) with ST-segment depression in lead II and anterolateral leads. There is a T-wave inversion in anterior leads and QTc prolongation of 471 ms [Figure 3a]. The fourth ECG tracing was taken within 3 days after ICU discharge showing NSR with normalization of the above ST-segment depression and QTc prolongation. There is a Wavy triple sign (Yasser's sign) in the V2 lead [Figure 3b]. Allergic angina with QTc prolongation and Wellens type-A syndrome post-ceftriaxone parallel

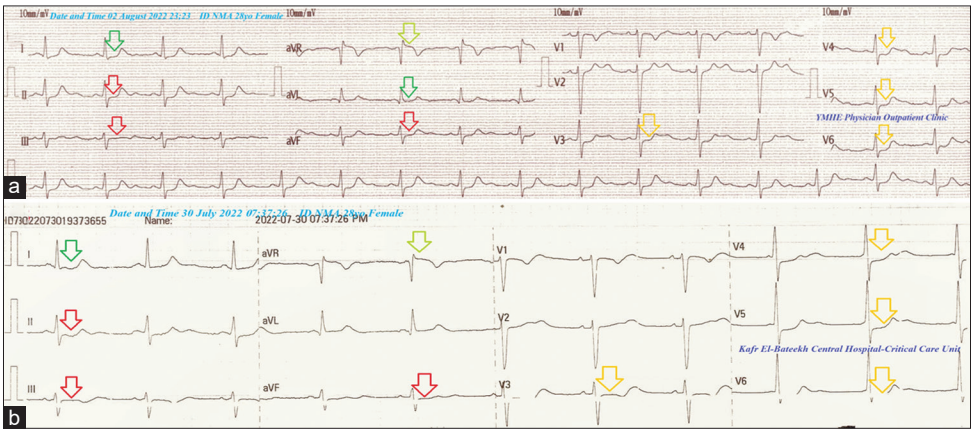

Figure 1: Serial ECG tracings; (a) tracing was done on the initial electrocardiography (ECG) on presentation in the point-of-care showing normal sinus rhythm (NSR) (ventricular rate [VR] of 72) with ST-segment depression in high lateral leads (I and aVL; green arrows) anterolateral leads (V3-6; golden arrows) and inferior leads (II, III, and aVF; red arrows). There is ST-segment elevation in aVR lead (lime arrow). (b) Tracing was done on the initial ECG on presentation within 30 min after intensive care unit admission showing NSR (VR of 62) with ST-segment depression in lead I (green arrow) anterolateral leads (V3-6; golden arrows), and inferior leads (II, III, and aVF; red arrows). There is ST-segment elevation in aVR lead (lime arrow)

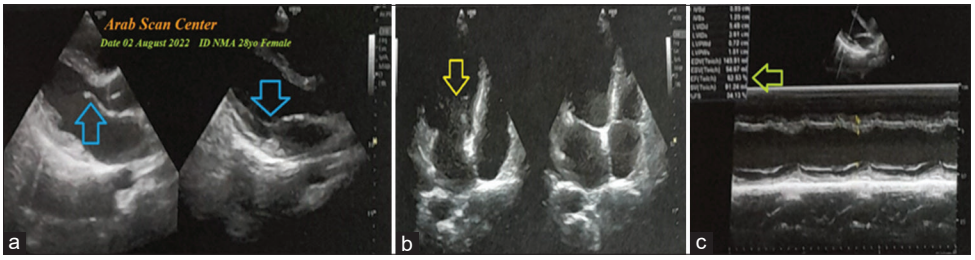

Figure 2: (a-c) Echocardiography was done on the 4th day of the presentation showing a mild thickened tip of anterior mitral valve leaflet prolapse (light blue arrows) and mild mitral regurgitation with eccentric jet (yellow arrow) of an ejection fraction of 62% (lime arrow)

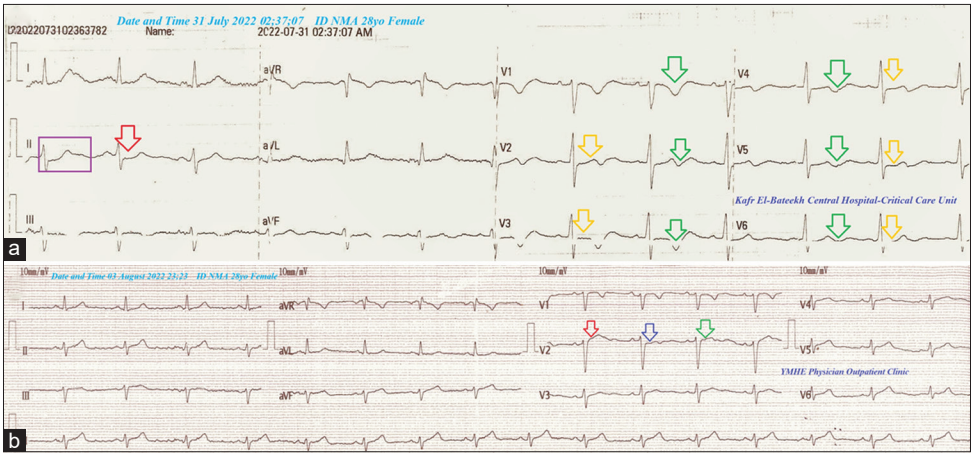

Figure 3: Serial electrocardiography tracings; (a) Tracing was done within 7 h of the intensive care unit (ICU) management showing normal sinus rhythm (NSR) (ventricular rate [VR] of 74) with ST-segment depression in anterolateral leads (V3-6; golden arrows) and lead II (red arrow). There is a T-wave inversion in anterior leads (V1-6; golden arrows) and QTc prolongation of 471 ms (purple rectangle). (b) Tracing was done within 3 days after ICU discharge showing NSR (VR of 71) with normalization of the above ST-segment depression and QTc prolongation. There is a Wavy triple sign (Yasser's sign) in V2 lead (red, dark blue, and green arrow)

to COVID-pneumonia was the most probable diagnosis. Within 3 days of the above management, the patient finally showed nearly complete clinical and ECG improvement. The patient was continued on aspirin tablets (75 mg, OD), diltiazem tablets (60 mg, OD), oral nitroglycerine capsules (2.5 mg, BID), oral calcium, and Vitamin-D preparations for 30 days with further recommended cardiac and immunological follow-up.

DISCUSSION

Overview

- A young married female patient was referred to the critical care unit with angina, QTc prolongation, and Wellens type-A syndrome post-ceftriaxone parallel to COVID-19 pneumonia
- The primary objective for my case study was the presence of a young married female patient who was referred to the critical care unit with angina, with QTc prolongation and Wellens type-A syndrome post-ceftriaxone parallel to COVID-19 pneumonia in ICU.

The secondary objective for my case study was the question of; how did you manage the case?

- There was a history of direct contact with a confirmed COVID-19 case
- The presence of direct contact with a confirmed COVID-19 case, clinical manifestations (fever, generalized body aches, loss of appetite, and loss of smell), and CBC evidence (leukocytosis, lymphopenia, and neutrophilia) of suspected COVID-pneumonia on top of acute tachypnea will strengthen the COVID-19 diagnosis
- There are initial high lateral leads, anterolateral leads, and inferior leads ST-segment depression

Table 1: Naranjo algorithm-adverse drug reaction probability scale in the case report

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	−1	0	+2
5. Are there alternative causes that could on their own have caused the reaction?	−1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	+1
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
			Total score: +11	

with elevated troponin I and subsequent T-wave inversion. This indicates the presence of extensive non-ST-segment elevation myocardial infarction (non-STEMI)

- QTc of 471 ms indicates the presence of LQTS
- There is ST-segment elevation in aVR lead. This has a different prognostic value
- The presence of extensive Non-STEMI with ST-segment elevation in aVR lead and T-wave inversion in anterolateral leads
- An existence of biphasic T-wave with the initial deflection positive and the terminal deflection negative is a hallmark of Wellens syndrome type A
- The presence of extensive non-STEMI with ST-segment elevation in aVR lead and T-wave inversion in anterolateral leads or Wellens syndrome type A may be interpreted as accompanied by severe specific ischemic myocardial insult
- Normalization of the above ST-segment depression may be evidence of CAS
- The later disappearance of the above ECG changes after management strengthens the role of included treatment
- The dramatic reversal of ST-segment depressions in ECG may be interpreted as a CAS
- Occurrence of angina after injection of ceftriaxone indicates its possible causation. Naranjo's probability scale in the current case study was +11. This means that there was a definite relationship between these adverse drug effects and ceftriaxone injection [Table 1]. KZ syndrome probably will be implicated in pathogenesis.
- I can't compare the current case with similar conditions. There are no similar or known cases with the same management for near comparison
- The only limitation of the current study was the unavailability of coronary angiography.

CONCLUSION AND RECOMMENDATIONS

- Ceftriaxone-inducing allergic ACS or KZ syndrome with QTc prolongation and Wellens type-A syndrome post-COVID-pneumonia is a distinctive new adverse effect
- The widespread non-STEMI with ST-segment elevation in aVR lead and T-wave inversion in anterolateral leads or Wellens syndrome type A may be interpreted as accompanied by multi-vessels disease.
- An associated COVID-19 infection may be an exacerbated factor for the ceftriaxone-inducing allergic ACS.

CONFLICT OF INTEREST

There are no conflicts of interest.

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