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Case Report

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Zavras-Kounis Type I Syndrome, Anaphylaxis, Wavy Double, and Wavy Triple Signs Post-Ceftriaxone-Responsive to Standard Anti-anaphylaxis

Yasser Mohammed Hassanain Elsayed*

Critical Care Unit, Kafr El-Bateekh Central Hospital, Damietta Health Affairs, Egyptian Ministry of Health (MOH), Egypt

***Corresponding Author**
Yasser Mohammed Hassanain Elsayed, Critical Care Unit, Kafr El-Bateekh Central Hospital, Damietta Health Affairs, Egyptian Ministry of Health (MOH), Egypt

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Abstract

Rationale: *Drug-inducing side effects are undoubtedly one of the most frequent entities in applied medicine. Drug-inducing allergic angina, allergic coronary spasm, and allergic infarction are different recognized as Zavras-Kounis syndrome. The Kounis–Zavras syndrome and allergic angina are designated as the simultaneous existence of angina and allergic reactions associated with clinical and laboratory signs of classical angina pectoris. Both the Wavy triple electrocardiographic sign (Yasser's Sign) and the related Wavy double sign (Yasser's Sign) are innovative diagnostic signs in hypocalcemia. A Wavy double electrocardiographic sign was prescribed in hypocalcemia which is mostly seen with either tachycardia or bradycardia. Ceftriaxone is a third-generation cephalosporin prescribed for several bacterial infections. World Health Organization considered it in the List of Essential Medicines.*

Patient concerns: *A 22-year-old married, security man, smoker, Egyptian male patient was admitted to the critical care unit with anaphylaxis and angina after an intravenous injection of ceftriaxone.*

Diagnosis: *Zavras-Kounis syndrome type I, anaphylaxis, Wavy double, and Wavy triple signs post-ceftriaxone injection.*

Interventions*: Electrocardiography, oxygenation, and echocardiography.*

Outcomes: *The dramatic disappearance of anaphylactic shock, Zavras-Kounis syndrome type I, and coronary spasm after the traditional treatment of anaphylaxis had happened. Complete clinical and electrocardiographic recovery had been achieved. Lessons: Ceftriaxone injection can induce anaphylactic shock, Kounis–Zavras type I syndrome, coronary spasm, and anaphylaxis. Kounis–Zavras type I syndrome, coronary spasm, and anaphylaxis can be reversed with treatment of the cause without using anti-ischemic or ant-arrhythmic measures. The identification of drug-induced disease is a pivotal step in the diagnosis and decision-making of any medical problems. Reassurance was recommended regarding ceftriaxone-induced coronary spasm accompanied by anaphylaxis.*

Keywords: Zavras-Kounis Syndrome, Allergic Coronary Disease, Wavy Double Sign, and Wavy Triple Sign, Hypocalcemia, Ceftriaxone, Third-Generation Cephalosporins, Adverse Effects.

Abbreviations

CAS: Coronary Artery Spasms
IMI: Inferior Myocardial Infarction
ECG: Electrocardiogram
ICU: Intensive Care Unit
KS: Kounis–Zavras Syndrome
MI: Myocardial Infarction
O2: Oxygen
SGOT: Serum glutamic-oxaloacetic transaminase
SGPT: Serum glutamic-pyruvic transaminase
STEMI: ST-segment elevation myocardial infarction
VR: Ventricular rate

1. Introduction

Kounis–Zavras (KS) syndrome or Allergic angina pectoris is marked as the concomitant presence of chest pain and allergic reactions linked to clinical and laboratory findings of typical angina pectoris. KS syndrome is caused by released inflammatory mediators during the allergic attack [1,2]. KS was originally named a Kounis and Zavras in 1991[3]. KS syndrome is covering the commonalty of the clinical spectrum of acute cardiac ischemia, from angina pectoris to acute myocardial infarction (AMI) in coincidence with an "allergic" (hypersensitivity, anaphylactic, or anaphylactoid) reaction [1,2]. Clinical manifestations are principally due to coronary artery spasms (CASs) [1,2]. Angina is clinically more prevalent than AMI [4]. Whilst the exact pathophysiological mechanisms are still obscure, released inflammatory mediators in anaphylactic reactions like to be the inducer in allergic angina or AMI [4]. There are known three variants of KS. Variant-I is the most common one (72.6%). But the emitted inflammatory mediators cause a CAS with or without an increase of cardiac enzymes and troponins. In variant II (22.3%), the produced inflammatory mediators, concurrently cause CAS with plaque rupture manifesting as AMI. Variant III (5.1%) involves patients with stented coronary artery thrombosis due to an allergic reaction. The treatment of the allergic reaction may be helpful for patients with the KS variant-I which, by itself can cure the cardiac symptoms [5]. To overcome the acute phase, these patients require corticosteroids, anti-histamines (both H1- and H2-blockers), fluid resuscitation, and eventually epinephrine, and not the standard therapy for MI (e.g. aspirin, heparin, β-blockers (BB), angiotensin-converting enzyme (ACE) inhibitors, statins, percutaneous coronary intervention (PCI), stent implantation) [6]. Anaphylaxis scarcely presents as an acute vasospastic coronary syndrome with or without ischemic heart disease (IHD) [7]. Ceftriaxone is an antibacterial β-lactam antibiotic, third-generation cephalosporin [8]. World Health Organization considered ceftriaxone in the List of Essential Medicines [9]. t is indicated in respiratory tract infections, urinary tract infections (UTIs), sexually transmitted diseases (TSD), septicemia, acute otitis media (AOM), bone infections, joint infections, endocarditis, GI infections, intra-abdominal infections, meningitis, and skin structure infections. It is given by IV or IM injection. Give intermittent IV infusions over 30 minutes (except for neonates). General adult dose; 1–2 g once daily or in equally divided doses twice daily. One manufacturer recommends 50–75 mg/kg every 12 hours (up to 2 g daily) for the treatment of serious infections other than meningitis. It is contraindicated in known hypersensitivity to ceftriaxone, any other cephalosporin, or a history of anaphylaxis to ceftriaxone, cephalosporins, penicillins, or other β-lactam anti-infectives. Hypersensitivity reactions, cross-hypersensitivity, gallbladder pseudolithiasis, urolithiasis and post-renal acute renal failure, pancreatitis, and seizures are reported side effects. Prolonged PT reported rarely [8]. Wavy triple an electrocardiographic sign (Yasser Sign) is a recently novel diagnostic sign innovated in hypocalcemia. Related Wavy double electrocardiographic sign also was prescribed in hypocalcemia which is mostly seen with either tachycardia or bradycardia [10,11].

The analysis for this sign in the author's interpretations is based on the following;

1. Different successive three beats in the same lead are affected.
2. All ECG leads can be implicated.
3. An associated elevated beat is seen with the first of the successive three beats, a depressing beat with the second beat, and an isoelectric ST-segment in the third one.
4. The elevated beat is either accompanied by ST-segment elevation or just an elevated beat above the isoelectric line.
5. Also, the depressed beat is either associated with ST-segment depression or just a depressing beat below the isoelectric line.
6. The configuration for depressions, elevations, and isoelectricities of the ST segment for the subsequent three beats are variable from case to case. So, this arrangement is non-conditional.
7. Mostly, there is no participation among the involved leads. The author intended that is not conditionally included in the special coronary artery for the affected leads8.

1.1. Aim of this Study

In this manuscript, I reported the development of Zavras-Kounis type I syndrome, anaphylaxis, Wavy double, and Wavy triple signs within 1 hour after ceftriaxone injection in a young-aged male patient.

1.2. Case Presentations

A 22-year-old, security man, smoker, Egyptian, married, male patient presented to the Emergency Department with transient loss of consciousness, generalized body itching, and chest pain. This had happened within one hour after the intravenous injection of ceftriaxone (1gm). Ceftriaxone was prescribed by a general

physician for acute upper respiratory tract infection. He is a heavy smoker (at least 20 cigarettes for about 3 years). He gave a past history of the same past attack. The patient denied any history of other cardiac, thyroid, or other relevant diseases. Informed consent was taken. Upon examination, the patient appeared stressed, flushed face with generalized hives, and swollen both lips, and eyelids. Tachypnea has been noted with generalized sibilant rhonchi was heard on chest examination. His vital signs were as follows: blood pressure of 90/70 mmHg, the pulse rate of 110/bpm; and regular, the respiratory rate of 22/min, the temperature of 37.3°C, the pulse oximeter of oxygen (O2) saturation of 91%, and tachycardia on heart auscultation. No more relevant clinical data were noted during the clinical examination. He was admitted to the intensive care unit (ICU) with anaphylaxis and acute severe chest pain. The initial urgent electrocardiogram (ECG) showed sinus tachycardia at 105 beats/min with ST-segment depression in the anterior (I, aVL, and V4-6) and inferior (II) leads, Wavy double sign, and Wavy triple sign of hypocalcemia. The patient was already connected to the ICU monitor for vitals and O2 saturation follow-up. Oxygen inhalation (5 L/min) was given. IM adrenaline 0.5 mg of 1:1000, IV hydrocortisone 200 mg, IV chlorpheniramine maleate 20 mg, IV normal saline 0.9% 500 ml, and IV Ringer solution 500 ml. One calcium gluconate ampoule (10 ml 10% over IV over 10 minutes) was given as an emergency dose. The second ECG tracing was done within 4 hours of the initiation of management with anti-allergic showing NSR at VR;98 beats/min with a Wavy double sign or Yasser's sign in V1 and V4 and Wavy triple sign or Yasser's sign-in V1 leads. Muscle spick artifacts are seen in aVR, aVL, and aVF leads with the reversal of the above ST-segment depressions (Figure 2A). The third ECG was done within 4 hours of the initiation of management with anti-allergic and within one minute of the above tracing showing NSR at VR; 97 beats/min with a Wavy double sign or Yasser's sign-in II and V4 leads and Wavy triple sign or Yasser's sign-in V1 lead with normalization of the above ST-segment depression (Figure 2B). The complete blood count showed only eosinophilia (13%). Plasma Na+:133 mmol/l, K+:3.8 mmol/L, and ICa++:0.8 mmol/L. Both CK-MB and troponin levels were negative. Random blood glucose: 177 mg/dl. Later echocardiography showed no detected abnormalities with EF 61%. The gradual dramatic response of anaphylaxis to anti-anaphylactic measures with clinical and electrocardiographic (sinus tachycardia and CAS) improvement had happened. The patient was discharged within 12 hours from management and after complete recovery. Zavras-Kounis type I syndrome, anaphylaxis, Wavy double, and Wavy triple signs post-ceftriaxone injection was the most probable diagnosis. IV Hydrocortisone (100 mg BID; for three days), oral chlorpheniramine maleate (8 mg BID; for three days), oral calcium, and vitamin-D preparation (for two weeks) were prescribed on discharge. The recommendation for future immunological consultation and follow-up. Allergy Cards and precautions were given with advice for future immunological consultation.

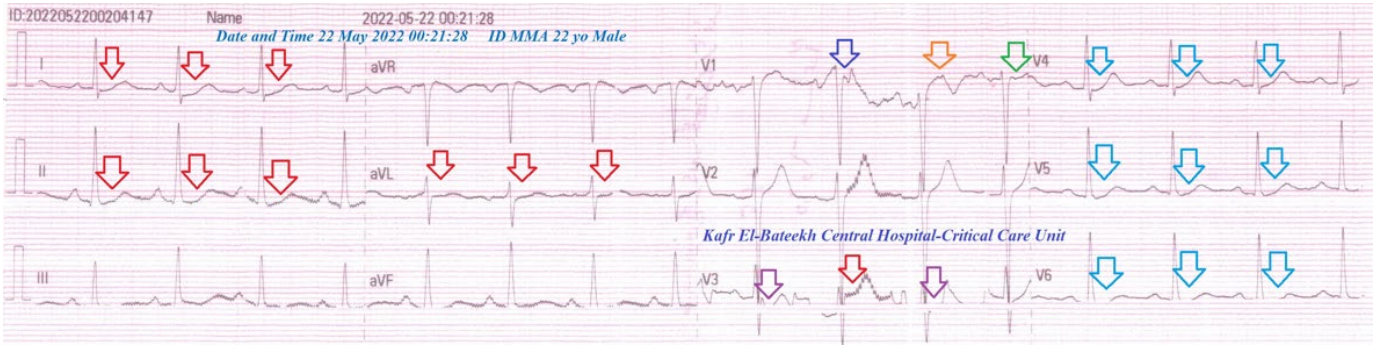

Figure 1: Serial ECG tracings; A. initial tracing was done on the presentation in the ICU showing sinus tachycardia at VR; 105 beats/min with ST-segment depression in the anterior (I, aVL, and V4-6; red and light blue arrows) leads and inferior (II; red arrows) ST-segment depressions, Wavy triple sign (V1; dark blue, orange, and green arrows), and Wavy double sign (V3; pink and red arrows) of hypocalcemia.

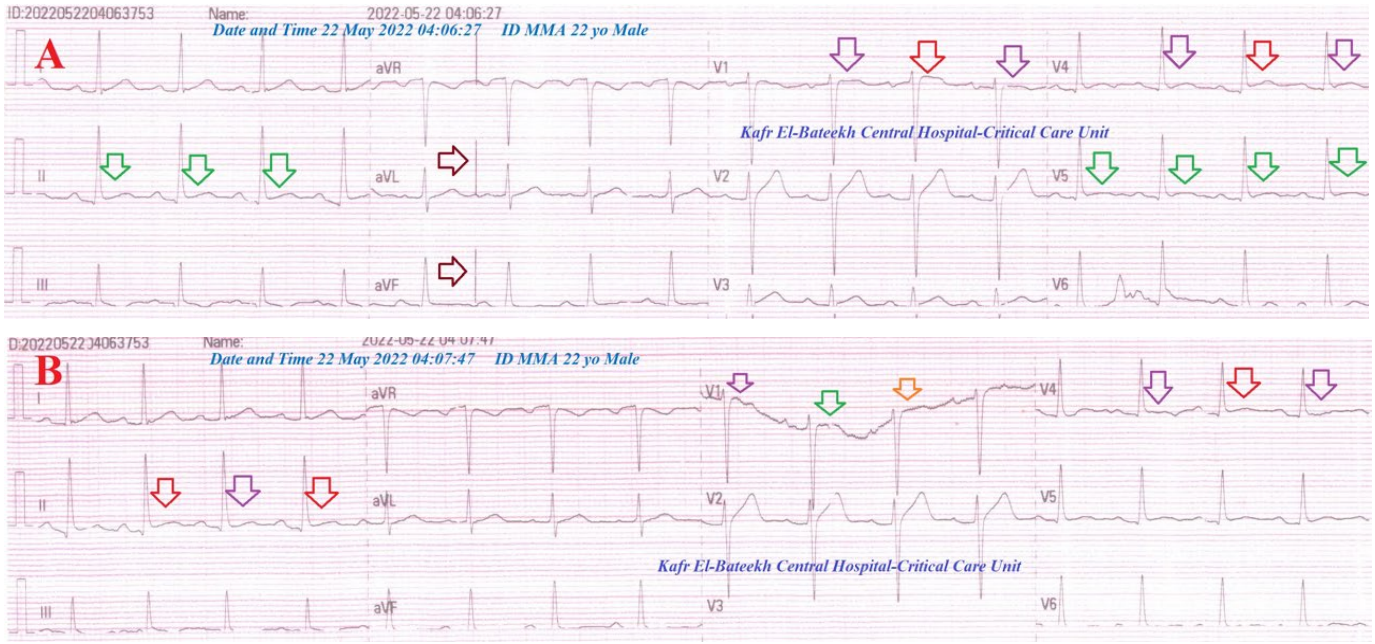

Figure 2 A-B: Serial ECG tracings; A. tracing was done within 4 hours of the initiation of management with anti-allergic showing NSR at VR;98 beats/min with a Wavy double sign or Yasser's sign in V1 and V4 (red and pink arrows) and Wavy triple sign or Yasser's sign-in V1 leads (pink, green, and orange arrows). Muscle spick artifacts are seen in aVR, aVL, and aVF leads (brown arrows) with the reversal of the above ST-segment depressions. There are ST-segment elevations in II and V5 (green arrows). B. tracing was done within 4 hours of the initiation of management with anti-allergic and within one minute of the above tracing showing NSR at VR;97 beats/min with a Wavy double sign or Yasser's sign in II and V4 leads (red and pink arrows) and Wavy triple sign or Yasser's sign-in V1 lead (pink, green, and orange arrows) with normalization of the above ST-segment depression.

Discussion

• **Overview;** The current case is a young-aged married male patient who presented to the ICU with anaphylactic shock and allergic angina within one hour after a ceftriaxone injection.

• **The primary objective** for the current case study was the presence of anaphylactic shock and KS type I syndrome in the ICU.

• After the exclusion of other possible triggers in the current case, **Naranjo's probability scale** was used to evaluate the association between ceftriaxone injection and the development of anaphylactic shock, KS type I syndrome, Wavy double, and Wavy triple signs. Naranjo's probability scale in the current case study was +11. It is meaning that there was a definite relationship between these adverse drug reactions and the causing drug; ceftriaxone vial. (Table 1).

- The secondary objective for the case study was; How would you manage anaphylactic shock, KS type I syndrome, Wavy double, and Wavy triple signs in ICU?
- The ECG ST-segment depressions which were reversed with anti-anaphylactic shock measures often indicate that this ischemic anginal insult is a coronary vasospastic abnormality of an allergic type (KS syndrome).
- Evidence of absence of ischemic heart disease in echocardiography directed that the variant of KS was KS type I syndrome
- Sinus tachycardia may interpret as a result of either a reflection of shock or hypoxia.
- KS type I syndrome, coronary spasm, and sinus tachycardia can be reversed with treatment of the cause without using anti-ischemic or ant-arrhythmic measures.
- Indeed, the mechanism of ceftriaxone injection inducing anaphylactic shock and KS type I syndrome with, Wavy double, and Wavy triple signs is unknown. The author thinks that shock, hypoxia, coronary artery spasm, and anxiety may be trigger factors.
- Despite the drug-drug interactions (DDIs) or even drug-food interactions having a strong impact in inducing various serious drug adverse effects, but, it was unviable in my case report. Absent of using drug combinations in the patient history may exclude the theory of drug-drug interactions.
- Finally, I reported the development of anaphylactic shock and Kounis type I syndrome with, Wavy double, and Wavy triple signs within 1 hour after using a ceftriaxone injection in a 22-year-old male patient.
- These Wavy double and Wavy triple signs can be interpreted as the current tachypnea that induces respiratory alkalosis and hypocalcemia.
- The main differential diagnoses for the study case are ST-segment elevation myocardial infarction (STEMI).

- **Limitations of the study**
- There are no known limitations in the study.
- **This is the first case that reports these adverse drug**

reactions with ceftriaxone injection.

- So, I can't **compare** this case with another case because there was no similar publicized case report.
- Drug-induced diseases is a pivotal step in the diagnosis and decision-making of any medical problems.
- Drug side effects are a sometimes-strong way to diagnose challenges in clinical medicine.

4. Conclusions

- Ceftriaxone injection can induce anaphylactic shock, Kounis–Zavras type I syndrome, coronary spasm, and anaphylaxis.
- The author thinks that Kounis–Zavras type I syndrome, coronary spasm, and anaphylaxis can be reversed with treatment of the cause without using anti-ischemic or ant-arrhythmic measures.
- Future precautions on using ceftriaxone injection, specifically, are the recommendation for the current case study.

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Conflicts of interest

There are no conflicts of interest.

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