

CASE REPORT

Kounis-Zafras Syndrome from Diclofenac Potassium: Novel ECG Signs Post-CABG

Yasser Mohammed Hassanain Elsayed

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

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

Abstract

Objective: This article aimed to clarify how diclofenac potassium can induce Kounis-Zafras syndrome from diclofenac potassium with novel ECG signs in patients who have undergone coronary artery bypass graft.

Introduction: Kounis-Zafras syndrome is an allergic acute coronary syndrome (ACS) following an allergenic exposure. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used to treat pain and inflammatory diseases. First-degree heart block or PR-interval prolongation is mostly an incidental electrocardiographic (ECG) sign with a characteristic prolonged PR-interval. Interestingly, Wavy triple and Wavy double ECG signs (Yasser's sign) are new specific diagnostic and therapeutic signs seen in the cases of hypocalcemia. Triphasic Yasser's stressor syndrome is a sequel and constellation of the vicious cycle of Yasser's Stressor test passing three stages in the form of fear, calm, and fear (Fear-Calm-Fear Yasser's syndrome). A coronary artery bypass graft (CABG) is evidence of a previously severe ischemic heart disease.

Methods: An observational-retrospective case report for a middle-aged married female diabetic patient was admitted to the intensive care unit with angina, PR-interval prolongation, Wavy triple, and Wavy double ECG signs after ingestion of diclofenac potassium in a previous coronary artery bypass graft (CABG).

Results: Diclofenac potassium-inducing Kounis-Zafras syndrome with intertwining first-degree heart block, Wavy triple sign, Wavy double sign (Yasser's signs), and Triphasic Yasser's stressor syndrome post-CABG in a middle-aged female diabetic patient.

Conclusion: A dramatic clinical, and electrocardiographic improvement had happened. Diclofenac potassium may be inducing Kounis-Zafras syndrome. An associated first-degree heart block with Triphasic Yasser's stressor syndrome after diclofenac potassium-inducing Kounis-Zafras syndrome are innovative cardiovascular findings. First-degree heart block, Triphasic Yasser's stressor syndrome, CABG, diabetes, Wavy triple sign, Wavy double sign (Yasser's signs), left ventricular hypertrophy, and female sex are constellation serious factors.

Keywords: Allergic Coronary Syndrome, Kounis-Zafras Syndrome, Wavy Triple Sign, Wavy Double Sign, Yasser's Sign, Hypocalcemia, Stress Test, Coronary Artery Spasm, Ischemic Heart Disease, Triphasic Yasser's Syndrome, Yasser's Stressor Test.

1. Introduction

Kounis-Zafras syndrome is a co-association of an acute coronary syndrome (ACS) with hypersensitivity reactions after exposure to allergens [1]. This

syndrome was initially described 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

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allergic, hypersensitivity, or anaphylactoid reactions [2]. The main pathogenesis of the syndrome 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 one hour of exposure to the offending allergen. Longer onset ACS also have been reported [3]. Variant presentations of the syndrome have been reported [2]. Three different variants of this syndrome 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 occurs in patients with pre-existing ischemic heart disease (IHD), in whom the acute release of inflammatory mediators induces CAS that may lead to plaque rupture and MI. Type III occurs in patients with coronary artery stent-associated thrombosis [1,3-5]. *Diclofenac* is a non-steroidal anti-inflammatory drug (NSAID) used to treat pain and inflammatory diseases. Increased risk of serious cardiovascular thrombotic events (e.g., angina, MI, and stroke). The risk may occur early in treatment and may increase with duration of use. Diclofenac is contraindicated in the cases of CABG surgery [6]. *First-degree atrioventricular block (AVB)* is a condition of abnormal slow conduction through the AV node. First-degree AVB is mostly an incidental electrocardiographic (ECG) sign with a characteristic PR-interval prolongation of more than 0.20 seconds [7]. Ischemic heart disease (IHD), myocardial infarction (MI), electrolyte disturbances (such as hypokalemia and hypomagnesemia), infective endocarditis, rheumatic fever, Chagas disease, Lyme disease, diphtheria, drugs (such as antiarrhythmics Ia, Ic, II, III, IV, digitalis, cholinesterase inhibitors), enhanced vagal tone (such as athletes), infiltrative diseases (such as sarcoidosis), collagen vascular diseases (such as SLE, rheumatoid arthritis, and scleroderma), idiopathic degenerative diseases (such as Lenegre and Lev diseases), and neuromuscular disorders are implicated causes of first-degree AV block [8,9]. *A wavy triple ECG sign (Yasser's sign)* is a new specific diagnostic sign seen in 97.3% of the cases of hypocalcemia [10]. *Wavy double ECG sign (Yasser's sign)* was also prescribed in hypocalcemia which is mostly seen with either tachycardia or bradycardia [10,11]. *Triphasic Yasser's syndrome* is a sequel and

constellation of the vicious cycle of Yasser's stressor test passing three stages in the form of fear, calm, and fear (Fear-Calm-Fear Yasser's syndrome) [12]. Coronary artery spasm is a possible pathogenesis for interpretation. Triphasic Yasser's syndrome is an easy, simple, cheap, and safe non-invasive exercise test [12]. Coronary artery bypass graft (CABG) is a surgical procedure to treat IHD. CABG is aimed at preventing death from IHD and improving quality of life by relieving angina [13].

In this article, I reported a case of diclofenac potassium-inducing Kounis-Zafras syndrome with intertwining first-degree heart block, Wavy triple sign, Wavy double sign (Yasser's signs), and Triphasic Yasser's stressor syndrome post-CABG in a middle-aged female diabetic patient. Wavy triple sign, Wavy double sign (Yasser's signs), and Triphasic Yasser's stressor syndrome are novel ECG signs that simultaneously appeared with Kounis-Zafras syndrome. These associated signs are not conditional to be relevant to Kounis-Zafras syndrome and were interpreted later in the discussion.

2. Case Presentation

2.1 History

A 57-year-old married housewife Egyptian female diabetic patient was admitted to the intensive care unit (ICU) with angina after ingestion of an oral diclofenac potassium tablet (100mg). The chest pain occurred within 60 minutes of the diclofenac potassium tablet which was prescribed for acute low back pain. Circumorally, numbness and extremities paresthesia were associated symptoms. She gave an old history of coronary artery bypass graft (CABG) 4 months ago after failure recurrent angina of PTCA and placed coronary artery stents.

2.2 Clinical Examination

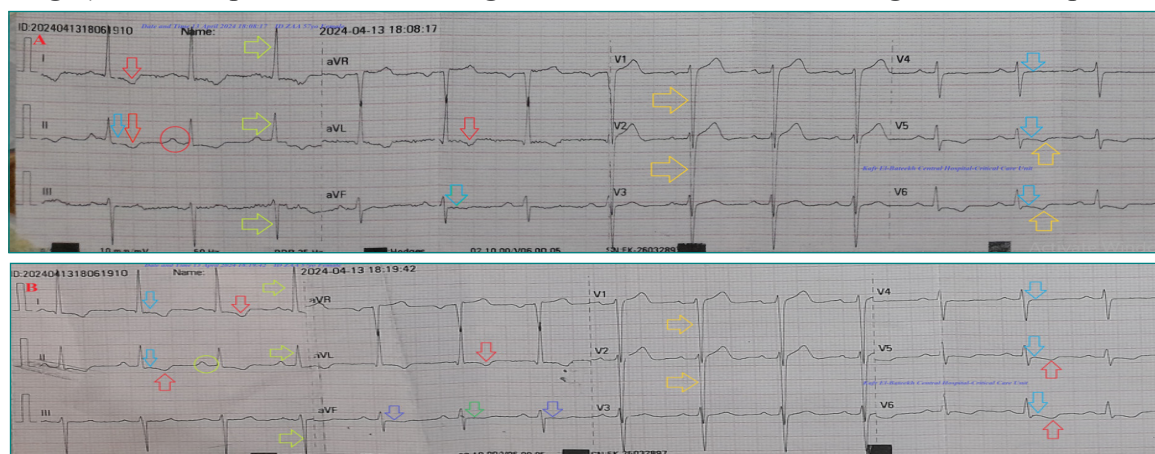
Upon general physical examination; generally, the patient was sweaty and distressed, with a regular pulse rate (VR of 80), blood pressure (BP) of 100/80 mmHg, respiratory rate of 16 bpm, a temperature of 36°C, and pulse oximeter of oxygen (O₂) saturation of 97%. Tests for provocative latent tetany were positive. No more relevant clinical data were noted during the clinical examination.

2.3 Investigations and Treatment

The patient was admitted to the ICU with oral diclofenac potassium-inducing angina. Initially, the patient was treated with O₂ inhalation by O₂ 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). The patient was hourly monitored for vital signs and O₂ saturation. The initial ECG was done on the initial ECG on presentation in the ICU showing normal sinus rhythm (NSR; of VR 82), with ST-segment depression with T-wave inversion in anterolateral and inferior leads, evidence of left ventricular hypertrophy (LVH) with strain, evidence of left axis deviation (LAD), and prolongation of PR-interval (*Figure 1A*). The second ECG tracing was taken within 11 minutes of the above ECG tracing and after ICU admission showing NSR (of VR 84) with Wavy double ECG sign (Yasser's sign), ST-segment depression with T-wave inversion in anterolateral and inferior leads, evidence of LVH with strain, evidence of LAD, and normalization of PR-interval (*Figure 1B*). The third ECG tracing was taken within 3 hours of the above ECG tracing and after ICU treatment showing NSR (of VR 83) with Wavy double ECG sign (Yasser's sign), normalization of the above ST-segment depression with still T-wave inversion in anterolateral and inferior leads, evidence of LVH with strain, and evidence of LAD (*Figure 1C*). The fourth ECG tracing was taken within 40 days of the above ECG tracing and after ICU treatment showing sinus tachycardia (of VR 102) with evidence of LVH with strain, evidence of LAD, and normal PR-interval (*Figure 1D*). The initial complete blood count (CBC); Hb was 12 g/dl, RBCs; $4.18 \times 10^3/\text{mm}^3$, WBCs; $10.8 \times 10^3/\text{mm}^3$ (Neutrophils; 60.9 %, Lymphocytes: 29.3%, Monocytes; 5.7%, Eosinophils; 4.1% and Basophils 0%), Platelets; $443 \times 10^3/\text{mm}^3$. SGPT was (19 U/L) and SGOT was (33 U/L). Serum creatinine was (0.8 mg/dl). RBS was (196 mg/dl). HbA1C was 10.2%. Total calcium was (8.61mg/d). Ionized calcium was (3.71mg/d). The troponin test was negative.

Echocardiography was done on 33 days before the ICU admission showing a fair LV systolic function of an EF of 53%, grade II diastolic dysfunction, and akinetic apex with apical to mid septum and anterior wall (*Figure 2A*). Echocardiography was done just after CABG showing a good LV systolic function of an EF of 61% and grade I diastolic dysfunction (*Figure 2B*). Another serial ECG tracings were done. The first ECG tracing was taken within 3 hours after ICU treatment showing NSR (of VR 79) with Wavy double ECG sign (Yasser's sign), ST-segment depression with T-wave inversion in anterolateral and inferior leads, evidence of LVH with strain, evidence of LAD, and normal of PR-interval (*Figure 3A*). The second ECG tracing was taken within 20 seconds of the above ECG tracing showing NSR (of VR 83) with a Wavy double ECG sign (Yasser's sign), normalization of the above ST-segment depression with still T-wave inversion in anterolateral and inferior leads, evidence of LVH with strain, and evidence of LAD), and prolongation of PR-interval (*Figure 3B*). The third ECG tracing was taken within the same minute of the above ECG tracing showing NSR (of VR 75) with Wavy triple ECG sign (Yasser's sign), normalization of the above ST-segment depression with still T-wave inversion in anterolateral and inferior leads, evidence of LVH with strain, and evidence of LAD, and normal of PR-interval (*Figure 3C*). Diclofenac potassium-inducing Kounis-Zafra syndrome with intertwining first-degree heart block, Wavy triple sign, Wavy double sign (Yasser's signs), and Triphasic Yasser's stressor syndrome post-CABG in a middle-aged female diabetic patient was *the most probable diagnosis*. Within 2 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.



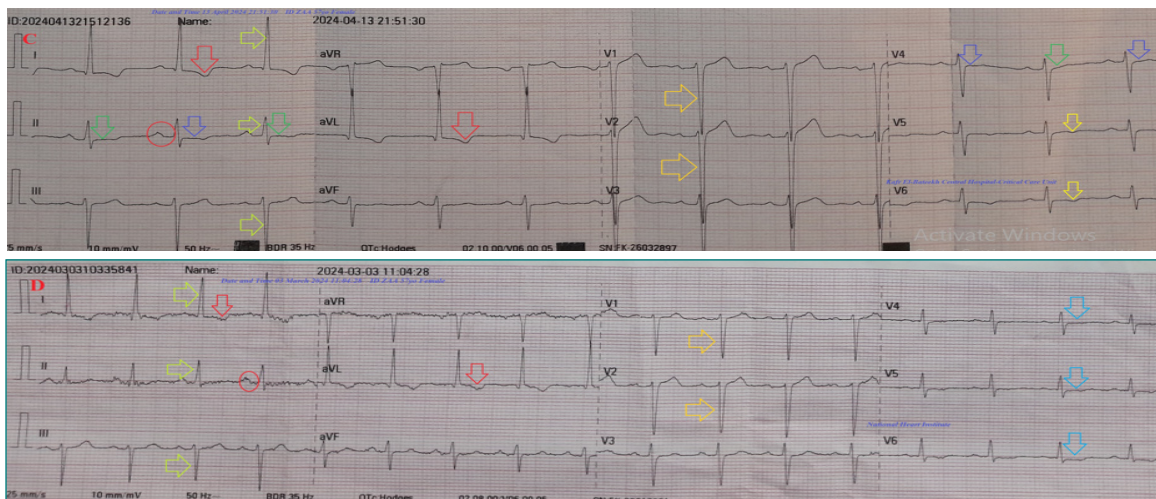


Figure 1 (A,B,C,D). Serial ECG tracings in the initial stage.

A. tracing was done on the initial ECG on presentation in the ICU showing NSR (of VR 82), with ST-segment depression (light blue arrows) with T-wave inversion (red arrows) in anterolateral and inferior leads, evidence of LVH (golden arrows) with strain, evidence of LAD (lime arrow), and prolongation of PR-interval (red circle). **B. tracing** was taken within 11 minutes of the above ECG tracing and after ICU admission showing NSR (of VR 84) with Wavy double ECG sign (Yasser's sign; aVF, dark blue and green arrows), ST-segment depression (light blue arrows) with T-wave inversion in anterolateral and inferior leads (red arrows), evidence of LVH (golden arrows) with strain, evidence of LAD (lime arrow),

and normalization of PR-interval (lime circle). **C. tracing** was taken within 3 hours of the above ECG tracing and after ICU treatment showing NSR (of VR 83) with Wavy double ECG sign (Yasser's sign; II and V4, dark blue and green arrows), normalization of the above ST-segment depression (light blue arrows) with still T-wave inversion (red arrows) in anterolateral and inferior leads, evidence of LVH (golden arrows) with strain (red arrows), and evidence of LAD (lime arrow). **D. tracing** was taken within 40 days of the above ECG tracing and after ICU treatment showing sinus tachycardia (of VR 102) with evidence of LVH (golden arrows) with strain (red arrows), evidence of LAD (lime arrow), and normal PR-interval (red circle).

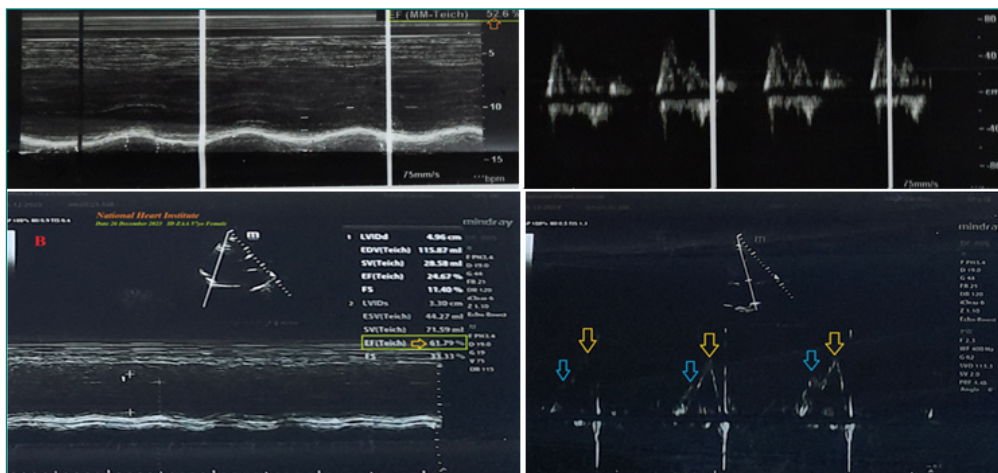
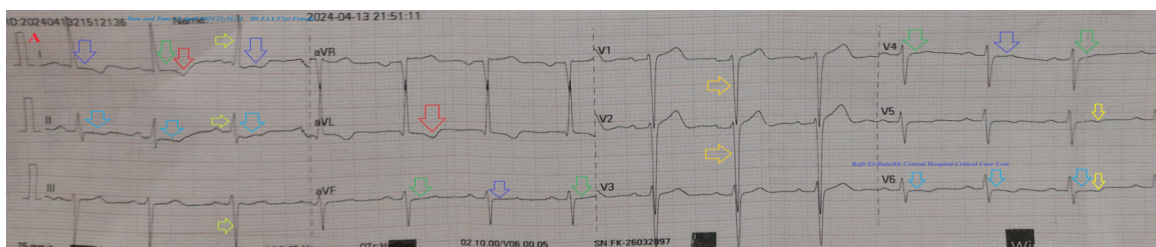


Figure 2. A. Echocardiography was done 33 days before the ICU admission showing a fair LV systolic function of an EF of 53% (golden arrow), grade II diastolic dysfunction, and akinetic apex (orange arrows) with apical to mid septum and anterior wall. B. Echocardiography was done just after CABG showing a good LV systolic function of an EF of 61% (golden arrow) and grade I diastolic dysfunction (light blue and orange arrows).



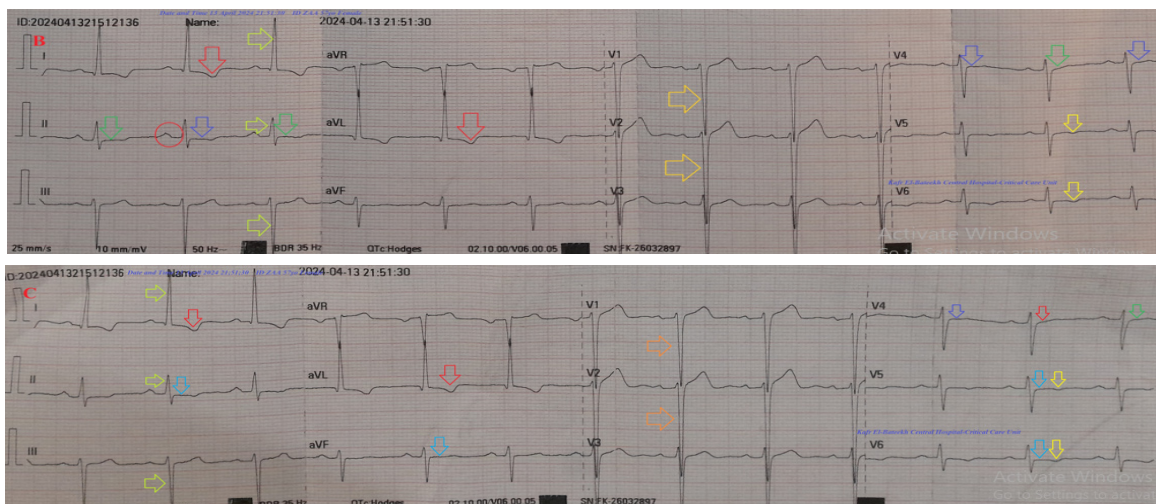


Figure 3. Serial ECG tracings taken within 3 hours after ICU treatment.

A. tracing was taken within 3 hours after ICU treatment showing NSR (of VR 79) with Wavy double ECG sign (Yasser’s sign; I, aVF, and V4, dark blue and green arrows), ST-segment depression (light blue arrows) with T-wave inversion (red arrows) in anterolateral and inferior leads, evidence of LVH (golden arrows) with strain (red arrows), evidence of LAD (lime arrow), and normal of PR-interval. **B. tracing** was taken within 3 hours after ICU treatment showing NSR (of VR 83) with Wavy double ECG sign (Yasser’s sign; II and V4, dark blue and green arrows), normalization of the above ST-segment depression (light blue arrows) with still T-wave inversion (red arrows) in anterolateral and inferior leads, evidence of LVH (golden arrows) with strain (red arrows), and evidence of LAD (lime arrow). **C. tracing** was taken within the same minute of the above ECG tracing showing NSR (of VR 75) with Wavy triple ECG sign (Yasser’s sign; V4, dark blue, red, and green arrows), normalization of the above ST-segment depression with still T-wave inversion (red arrows) in anterolateral and inferior leads, evidence of LVH (golden arrows) with strain (red arrows), and evidence of LAD (lime arrow), and normal of PR-interval.

3. Discussion

Overview

- A middle-aged married female diabetic patient was admitted to the ICU with angina, PR-interval prolongation, Wavy triple, and Wavy double ECG signs after ingestion of diclofenac potassium in a previous CABG.
- *The primary objective* for my case study was the presence of a middle-aged married female diabetic patient with angina, PR-interval prolongation, and Wavy triple, and Wavy double ECG signs after

ingestion of diclofenac potassium in a previous CABG in the ICU.

- *The secondary objective* for my case study was the *question* of how would you manage the case?
- The presence of angina after oral ingestion of diclofenac potassium in a previous CABG will strengthen the diagnosis of type II Kounis-Zafras syndrome which is an allergic ACS [1,3-5].
- The current initial prolongation of PR-interval indicates the presence of first-degree atrioventricular block. *First-degree atrioventricular block (AVB)* is a condition of abnormal slow conduction through the AV node. First-degree AVB is mostly an incidental electrocardiographic (ECG) sign with a characteristic PR-interval prolongation of more than 0.20 seconds [7].
- The disappearance prolongation of PR-interval or first-degree atrioventricular block confirmed that the problem is transient. The normalization of PR interval after a few minutes of inhaled oxygenation may be directed to the hypoxia due to an ischemic event.
- Clinically, tachypnea, numbness, and paresthesia of extremities with positive tests for latent tetany, laboratory lower ionized calcium, Wavy double ECG sign, and Wavy triple ECG sign (Yasser’s signs) are more parallel to hypocalcemia (Figure 1B, 1C, 3A, and 3C).
- The changeable of affected leads from ECG tracing to another tracing in the Wavy double ECG sign will be a signal to the diagnosis of Movable phenomenon or Yasser’s phenomenon of hypocalcemia (Figure 1B, 1C, 3A, and 3C).
- Movable phenomenon or Yasser’s phenomenon of

hypocalcemia is a signal for associated tachypnea in the current case.

- The presence of a changeable Wavy triple sign in ECG is a hallmark of the *Movable phenomenon* (Yasser's phenomenon) of hypocalcemia [11]. *The Wavy triple ECG sign* (Yasser's sign) is a recently innovated diagnostic sign in hypocalcemia [10]. The author's interpretations are 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 a special coronary artery for the affected leads [10,11].
- Tachypnea was a possible cause of hypocalcemia and subsequent Wavy triple ECG sign, Wavy double ECG sign, and Movable-weaning phenomenon of hypocalcemia [10,11].
- There is ST-segment depression then normalization of ST-segment depression. Then re-again ST-segment depression supports the diagnosis of Triphasic Yasser's stressor syndrome. *Triphasic Yasser's syndrome* is a sequel and constellation of the vicious cycle of Yasser's stressor test passing three stages in the form of fear, calm, and fear (Fear-Calm-Fear Yasser's syndrome) [12].
- The dramatic reversal of ST-segment depressions in ECG may be interpreted as a coronary artery spasm.
- The recurrent angina after CABG may be a hallmark of coronary artery restenosis.
- Acute pulmonary embolism is the most implicated *differential diagnosis*. The history and clinical data against it.
- This case added new signs post diclofenac potassium such as Wavy triple sign, Wavy double

sign (Yasser's signs), and Triphasic Yasser's stressor syndrome rather than Kounis-Zafras syndrome with first-degree heart block.

- 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 a new coronary angiography.

4. Conclusion and Recommendations

- Diclofenac potassium may be inducing clinical evidence of Kounis-Zafras syndrome.
- An associated first-degree heart block with Triphasic Yasser's stressor syndrome after diclofenac potassium-inducing Kounis-Zafras syndrome is evidence of innovative ECG cardiovascular findings.
- First-degree heart block, Triphasic Yasser's stressor syndrome, CABG, diabetes, Wavy triple sign, Wavy double sign (Yasser's signs), left ventricular hypertrophy, and female sex are constellation serious factors.

Conflicts of interest

There are no conflicts of interest.

Acknowledgment

I wish to thank my wife for saving time and improving the conditions for helping me.

Abbreviations

- ACS: Acute coronary syndrome
- AMI: Acute myocardial infarction
- AVB: Atrioventricular block
- CABG: Coronary artery bypass graft
- CAS: Coronary artery spasm
- CBC: Complete blood count
- ECG: Electrocardiography
- IV: Intravenous
- IHD: Ischemic heart disease
- ICU: Intensive care unit
- LAD: Left axis deviation
- LVH: Left ventricular hypertrophy
- Non-STEMI: Non-ST-segment elevation myocardial infarction
- NSAID: Non-steroidal anti-inflammatory drug

NSR: Normal sinus rhythm

MI: myocardial infarction

O2: Oxygen

VR: Ventricular rate

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