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Unraveling the Complexities of T wave Alternans and QT Prolongation in Advanced Chronic Kidney Disease: A Case Report and Literature Review

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ABSTRACT

The recognition of QT interval prolongation and T-wave alternans (TWA) on an electrocardiogram (ECG) is a critical prognostic criterion. We report a 78-year-old patient with advanced chronic kidney disease (CKD) to demonstrate the intricate interaction of variables leading to electrical instability in this demographic, in addition to stressing the relevance of comprehensive diagnostic and therapeutic techniques. We underline the significance of TWA and QT prolongation as indicators for imminent ventricular arrhythmias and sudden cardiac death (SCD). The case underscores the multifactorial causes of QT prolongation and TWA in CKD. It highlights the need for further research to understand the underlying mechanisms better and develop strategies to mitigate risks in CKD patients.

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KEYWORDS:

T-wave alternans, QT prolongation, chronic kidney disease, ventricular arrhythmias, sudden cardiac death, electrolyte imbalance, hemodialysis.

INTRODUCTION

T-wave alternans (TWA), a phenomenon characterized by beat-to-beat alternation in the morphology and/or magnitude of the T-wave on a 12-lead electrocardiogram (ECG), has emerged as a potent marker of electrical instability within the myocardium. First described in the early 1900s, TWA has been consistently associated with an increased risk of ventricular arrhythmias and sudden cardiac death (SCD)^(1,2,3,4). Concomitantly, QT interval prolongation, representing an extended duration of ventricular repolarization, has been implicated in the genesis of potentially life-threatening ventricular tachyarrhythmias, which may manifest as syncope, sudden cardiac arrest or death5.

The co-existence of macroscopic TWA and QT prolongation, although infrequent, has been observed in cases of long QT syndrome. The precise mechanisms linking long QT syndrome to TWA remain elusive; however, alterations in primary sarcolemmal ion currents are posited to play a pivotal role3. Notably, TWA is not exclusively confined to long QT syndrome and may manifest in various other pathologies.

Herein, we present a case study of a 78-year-old male with advanced chronic kidney disease (CKD) who presented with electrolyte imbalance and uremia. His ECG revealed striking findings of QT prolongation and macroscopic TWA. This case underscores the complex interplay of factors contributing to electrical instability in patients with advanced CKD. It highlights the critical importance of TWA interpretation as a harbinger of impending ventricular arrhythmia. Furthermore, it emphasizes the necessity of a comprehensive diagnostic approach when evaluating the multifactorial nature of QT prolongation and the paramount importance of vigilant ECG monitoring, meticulous electrolyte assessment, and prudent management to optimize outcomes in patients with advanced CKD.

CASE REPORT

A 78-year-old male with a history of diabetes mellitus, hypertension (HTN), atrial fibrillation (AF), dyslipidemia, and anemia secondary to advanced chronic kidney disease (CKD) was brought to the emergency department (ED) by his son. The patient complained of

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progressive fatigue for one week and palpitations for one day. He denied chest pain, dyspnea, paroxysmal nocturnal dyspnea, orthopnea, syncope, or dizziness. The patient had contact with sick individuals at home who had flu-like symptoms. There was no history of exposure to new medications or substances and no change in living arrangements. However, he had not taken his usual home medications (Table 1).

Physical examination revealed the patient was afebrile with an HR of 70 beats/min, no hemodynamic instability, a blood pressure (BP) of 167/119 mmHg, mild tachypnea, and an oxygen saturation of 98% without supplemental oxygen. The cardiac examination showed an irregular pulse without scars of previous cardiac surgery on the chest and no murmurs or heave.

A 12-lead ECG in the ED (Figure 1) confirmed the presence of AF with an HR of 70 beats/min, infrequent premature ventricular contractions (PVCs), and non-specific T wave changes. The QT interval was prolonged to 692ms, corresponding to a QTc of 719ms. Additionally, there was a variation in the amplitude and shape of the T waves suggestive of microvolt T wave alternans (TWA). Initial laboratory results (Table 2) showed potassium at the high end of the normal range and worsening renal function tests from the baseline in addition to normal levels of Serum Adjusted Calcium and magnesium with high phosphorus levels; a careful review of the patient Trend for Thyroid-stimulating Hormone (TSH) level were within the standard baseline, excluding thyroid disorder, A Baseline ECG obtained from patient records showed AF with HR of 80 beats/min, QT/QTc of 384ms/446ms and no TWA (Figure 2)

The patient was treated with his usual home medications (Nifedipine 60 mg and Bisoprolol 5 mg daily) for better BP control, oral kayexalate with insulin HR intravenously, and lactulose solution to further reduce potassium levels. A total of 4 grams of intravenous magnesium sulfate were infused to prolong QTc and TWA.

During admission, a repeat ECG (Figure 3) showed an AF rhythm with an HR of 80 beats/min and improvement in QT and QTc prolongation from 692ms to 488ms and from 719ms to 626ms, respectively, with a reduction in the amplitude of the observed TWA in the anterolateral chest leads.

The next day, another ECG (Figure 4) showed an HR of 80 beats/min in AF rhythm with further reduction in the QT/QTc duration to 502 ms /572 ms; no further TWA was observed while new laboratory investigations showed a decrease of serum potassium in addition to Adjusted Ca and an increase in magnesium and phosphorus level. Meanwhile, Bisoprolol was reduced to 2.5mg due to slow heart rate and tightly controlled blood pressure readings.

An echocardiogram during the admission showed biatrial enlargement with concentric LVH and no regional wall motion abnormalities. The patient was continued on other medications and was later discharged on his home medications in addition to oral magnesium maintenance.

A follow-up clinic visit with a new ECG (Figure 5) showed an HR of 93 beats/min in AF with no evidence of TWA and a QTc of 529 ms while continuing Bisoprolol 2.5 mg daily with oral magnesium replacements.

The patient eventually initiated hemodialysis after three months of worsening CKD. Subsequent ECGs showed no evidence of new findings with recurrence of the long QT/QTc interval (516ms/528ms at HR of 63 beats/min) and coexistence of TWA (Figure 6) in association with worsening laboratory investigations or slower heart rate (Table 3) and improving QT/QTc interval prolongation (444ms/479ms at HR of 66 beats/min) after HD initiation (Figure 7). This presentation is consistent with a multifactorial acquired QT/QTc prolongation probably secondary to renal disease progression, increased d serum creatinine and uremic toxin accumulation, and hypomagnesemia without drug-inducing QT/QTc prolongation.

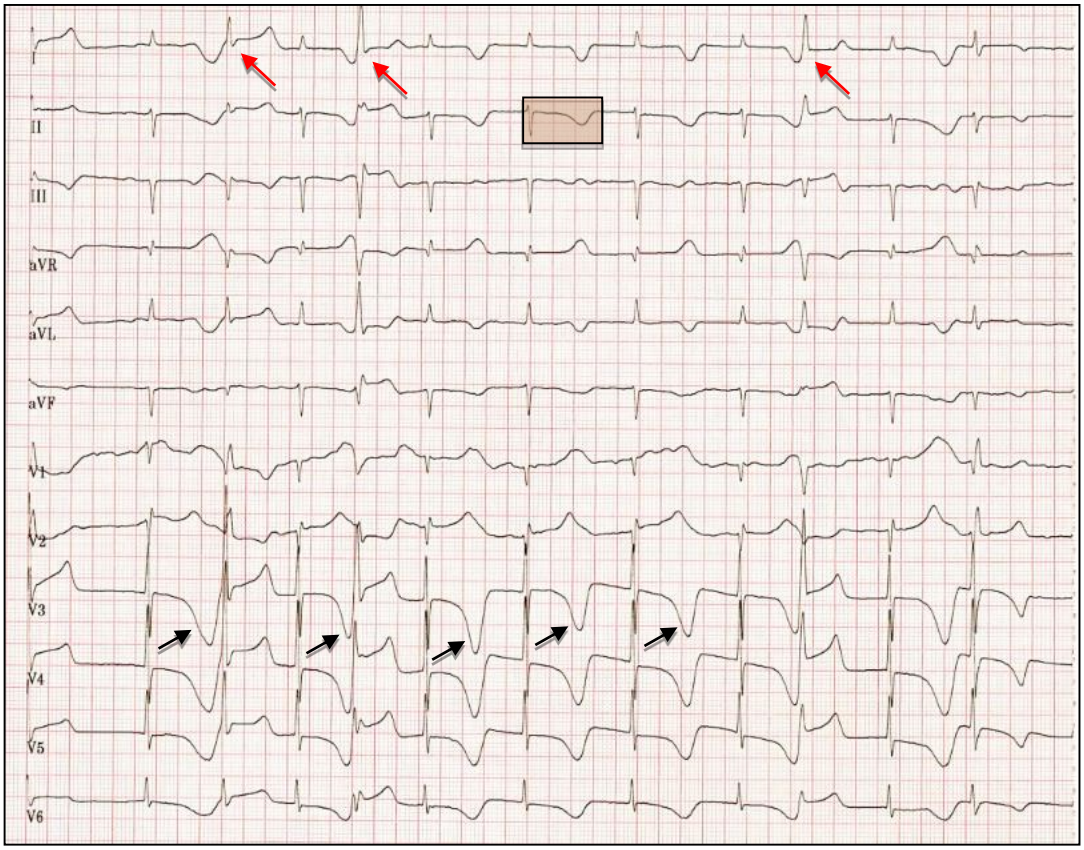

Figure 1 - ECG : AF Rhythm at HR of 70 beats/min revealing Macroscopic TWA, and PVCs on T waves – red arrows, black arrows respectively with prolonged QTc interval 719ms (red square).

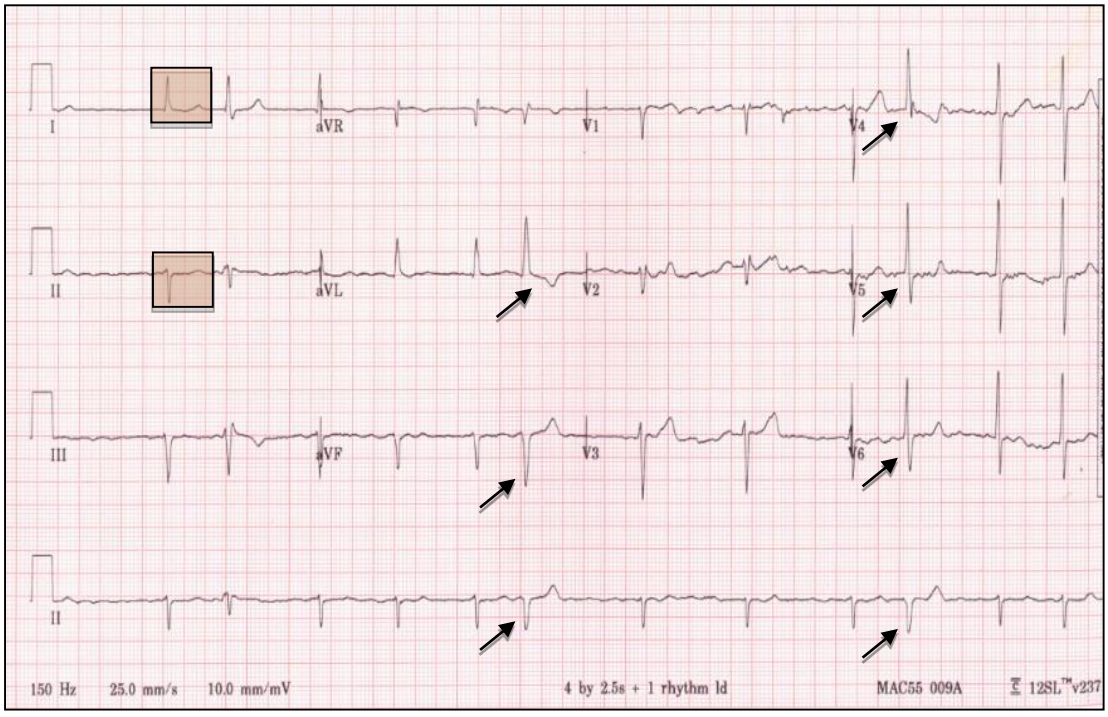

Figure 2 – ECG: A Baseline ECG obtained from patient records (3 years ago) showed AF with HR of 80 beats/min, QTc interval of 446 ms (Red square) and few PVCs (Black arrows)

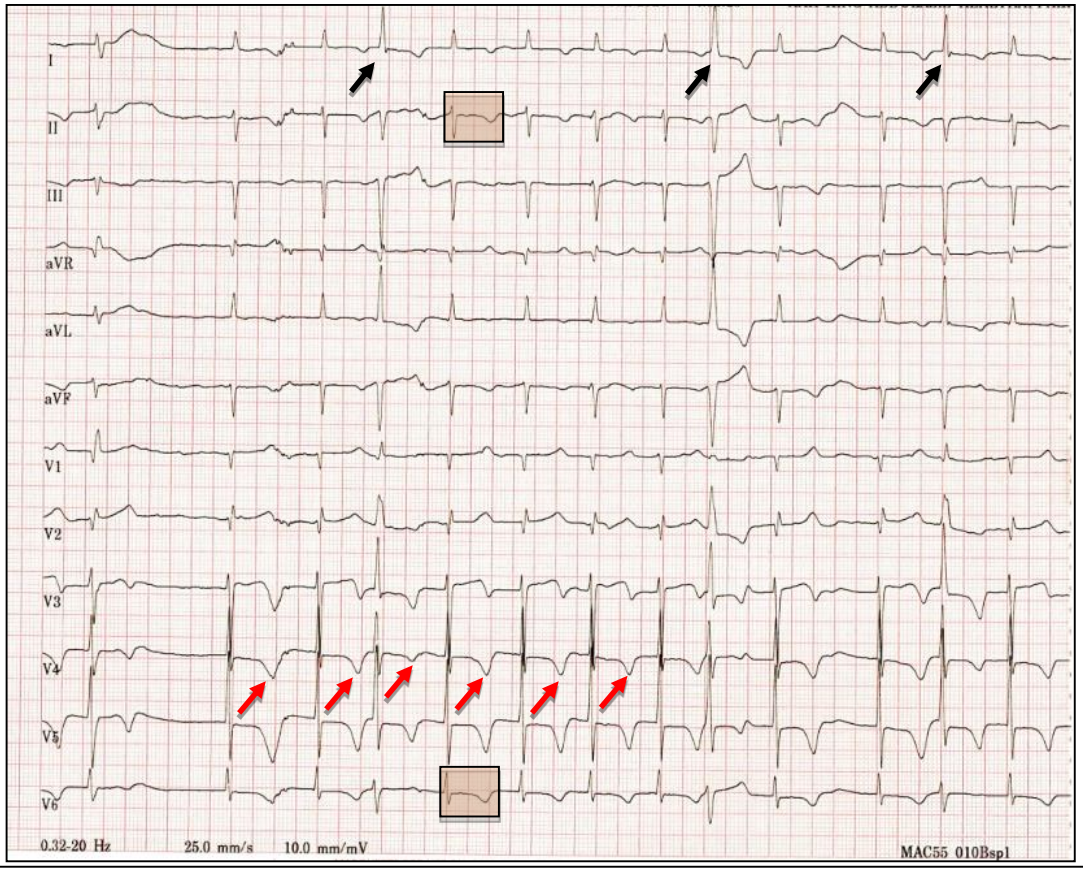

Figure 3 – ECG : AF Rhythm at HR of 80 beats/min showing improved Macroscopic TWA (Red arrows), Shortening QTc interval to 626ms (Red squares) and PVCs following T waves (black arrows)

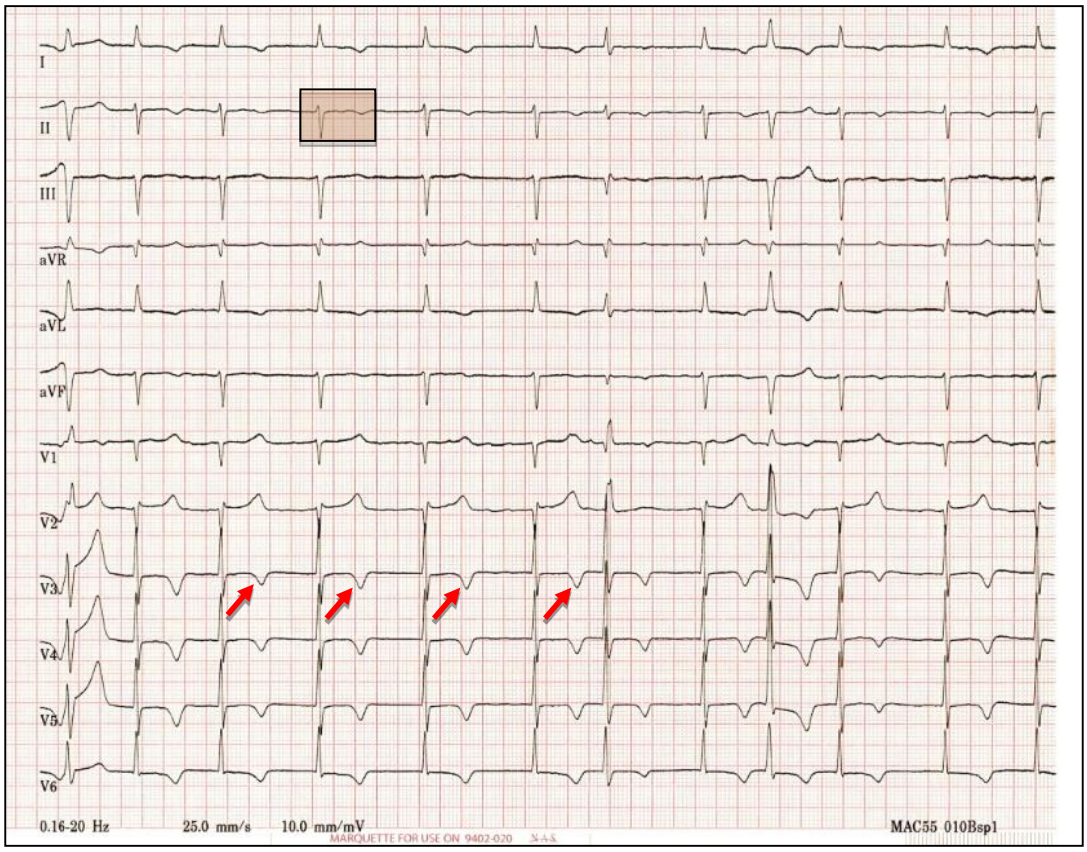

Figure 4 – ECG : AF Rhythm at HR of 80 beats/min showing no Macrovolt TWA (Red arrows), QTc interval 572ms (Red square) and no PVCs.

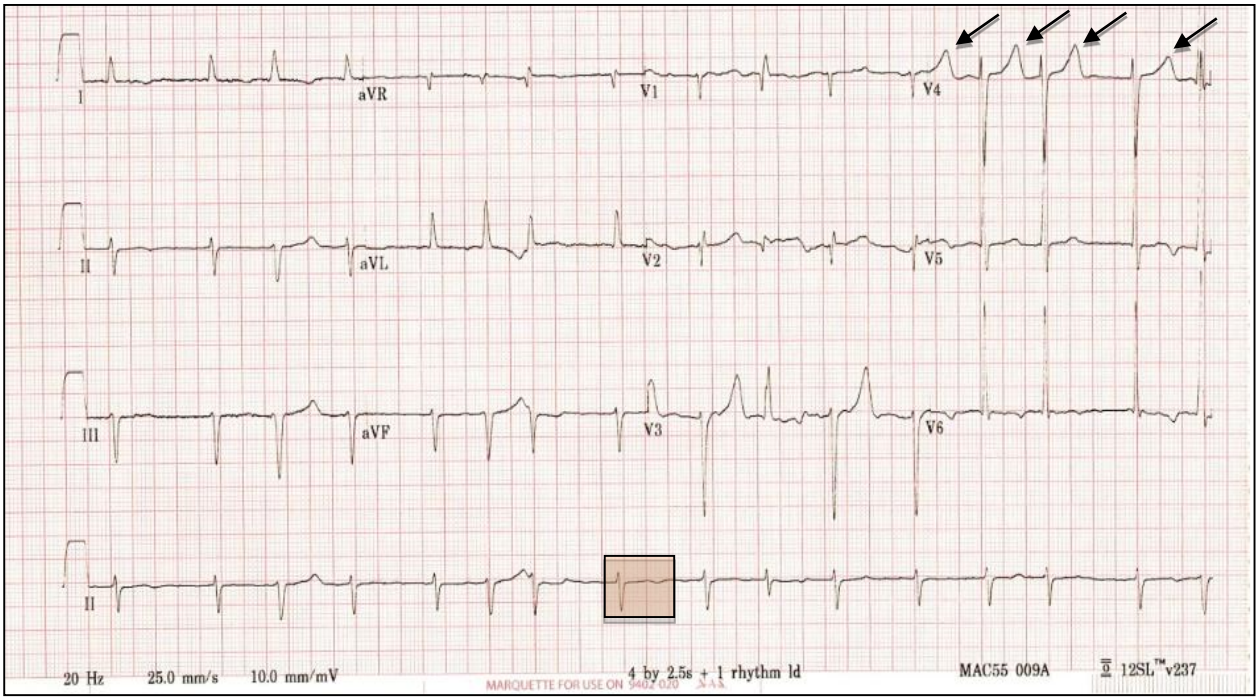

Figure 5 – ECG : AF Rhythm at HR of 92 beats/min showing no Macroscopic TWA (Black arrows), QTc interval 529ms (Red square) and no PVCs.

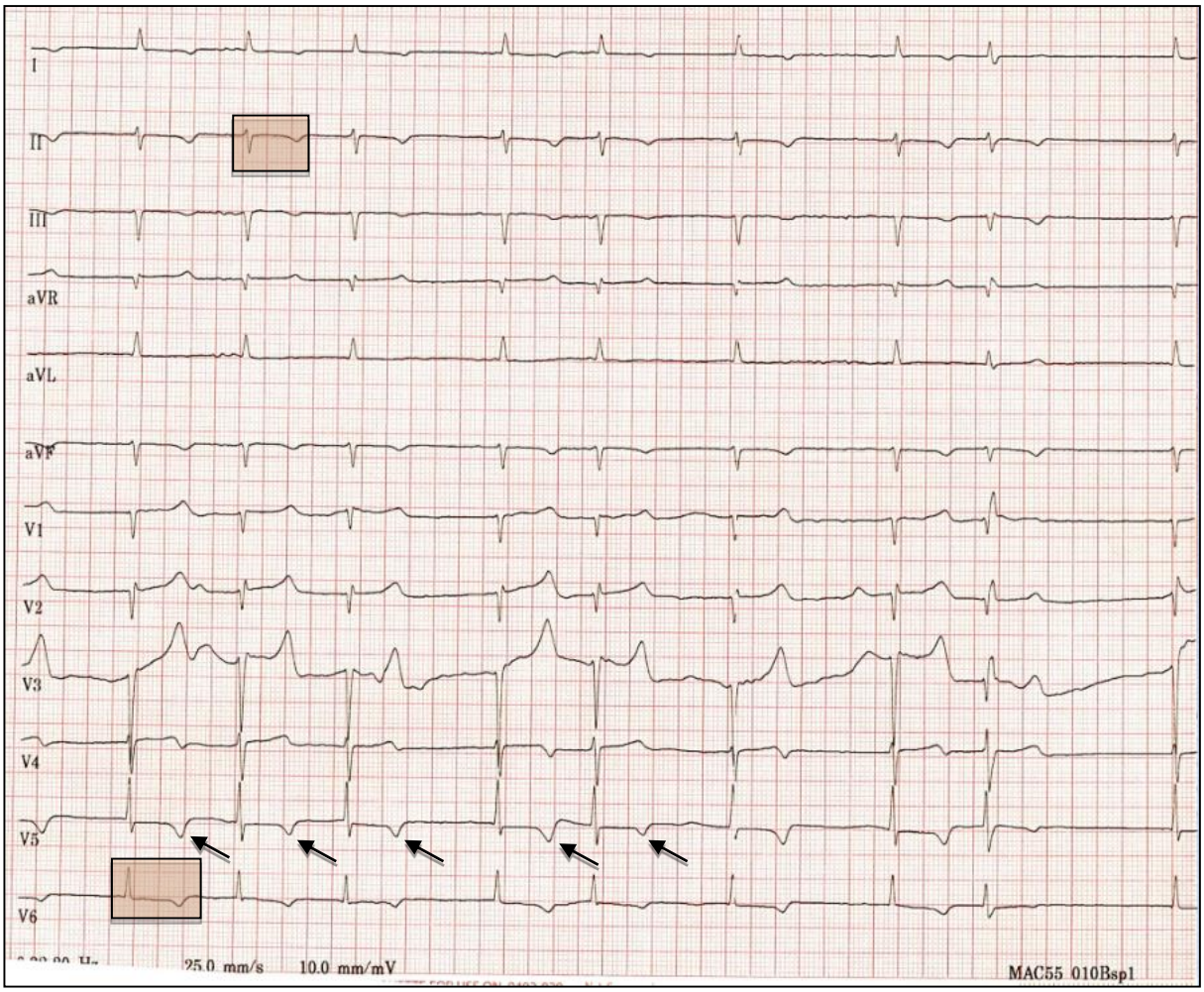

Figure 6 – ECG : AF Rhythm at HR of 63 beats/min showing Macroscopic TWA (Black arrows), QTc interval 528ms (Red square) and no PVCs shortly before patient's first Hemodialysis session.

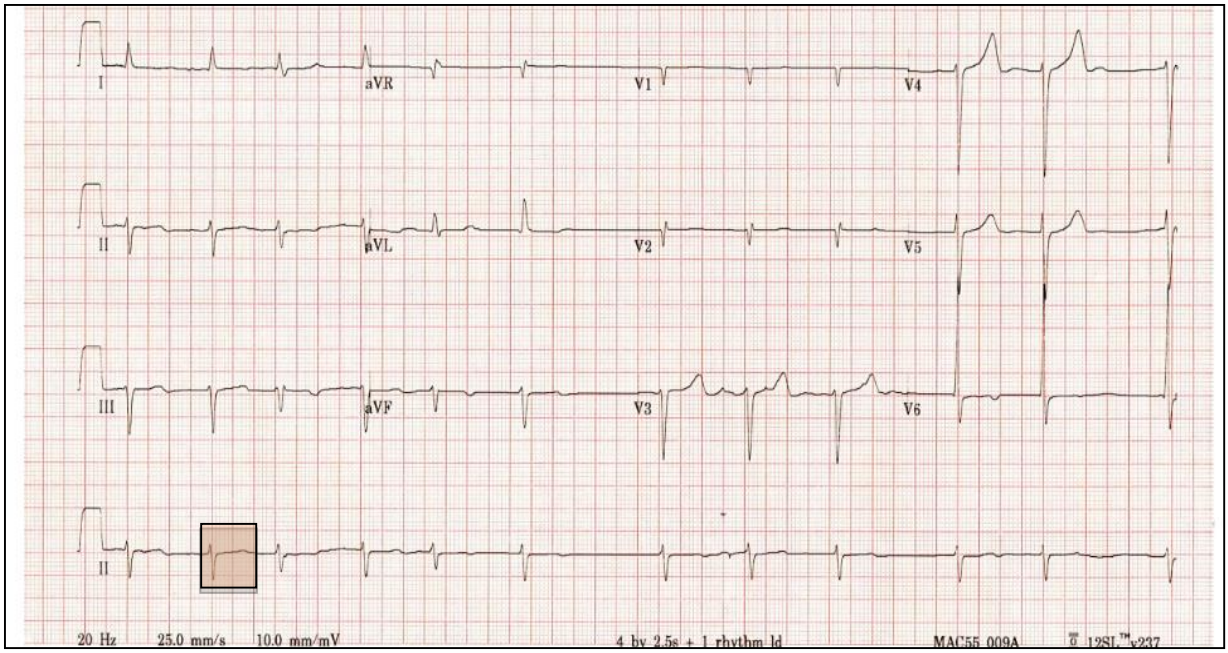

Figure 7 – ECG : AF Rhythm at HR of 66 beats/min showing no Macroscopic TWA nor PVCs and QTc interval of 479ms (Red square) after Hemodialysis initiation.

Table 1		Dose	Frequency
Medication Name / Form	Sodium Bicarbonate Tablet	1300 mg	TID
	GlipiZIDE Tablet	5 mg	OD
	CloNIDineTablet	0.1 mg	BID
	NIFEdipine ER Tablet	60mg	OD
	bisOPROLOl Fumarate Tablet	5mg	OD
	Ferrous Sulfate Tablet	1 tablet	BID
	Alfacalcidol Capsule	0.5 mcg	OD
	Multivitamin Tablet	1 tablet	OD
	Omeprazole Capsule	20 mg	OD
	Furosemide Tablet	80 mg	BID

Table 1 – Patient's home medications list with intake frequency and route, none of which can cause QT prolongation

Table 2	First day	Second day	Before HD	After HD
eGFR	12	11	6	20
Creat	448	487	784	286
BUN	30.2	30.9	36.6	9.4
Mg	0.77	1.14	0.86	0.8
K	5	4.7	6.3	4.3
Na	137	139	144	
CL	104	103	108	
Phos	1.96	2.19	2.67	1.08
ADJ Ca	2.37	2.24	2.39	2.35

Table 2 – Select Laboratory results, eGFR; estimated glomerular filtrate rate, Creat; Serum Creatine, BUN; Serum Blood urea level, Mg; Serum magnesium level, K; Serum potassium level, Na; Serum sodium level, CL, Serum chloride

level, Phos; Serum phosphorus level, ADJ Ca; Serum adjusted calcium (unit; mmol/L)

Table 3	Mg	K	Adj Ca	eGFR	BUN	Creatinine	HR
First day	0.77	5	2.37	12	30.2	448	70 BPM
QT/QTc	Prolonged to 692 ms / 719 ms						
TWA	Pronounced in timing and amplitude						
Second day	1.14	4.7	2.24	11	30.9	487	80 BPM
QT/QTc	Prolonged to 502 ms / 572 ms						
TWA	Less pronounced in timing and amplitude						
Before HD	0.86	6.3	2.39	6	36.6	784	63 BPM
QT/QTc	Prolonged to 516 ms / 528 ms						
TWA	Observed mainly on amplitude and shape						
After HD	0.8	4.3	2.35	20	9.4	286	66 BPM
QT/QTc	Prolonged to 444 ms / 479 ms						
TWA	Not Observed						

Table3 -Duration of QT/QTc in addition to presence of TWA during different intervals of patient's heart rate (HR) with serum electrolytes and renal functions, (unit; mmol/L), (BPM; beat per minute)

DISCUSSION

TWA and QT prolongation are reliable markers of the heart's electrical instability for predicting future ventricular arrhythmias, such as the life-threatening polymorphic torsade de pointes. TWA, a beat-to-beat T-wave alternation, may be visible and rare (Macroscopic TWA) or common but only detectable using special equipment and methods (Microvolt TWA)[6]. QT interval prolongation refers to a delay in the time for the heart's ventricles to recharge between beats, indicating slower than normal ventricular repolarization. Both TWA and QT prolongation are of particular concern in patients with advanced CKD, as this population often has multiple risk factors that can exacerbate electrical instability and lead to conduction abnormalities[7]. Additionally, several studies have described lengthening of the QT interval with declining renal function and advancing CKD stages[7,8].

Risk Factors for QT Prolongation in CKD

1. Diabetes mellitus (DM):

DM is one of the leading factors for QTc prolongation in CKD and accounts for 30% - 50% of CKD cases worldwide[9]. DM leads to numerous metabolic abnormalities that can cause alterations in electrolyte balance and hypertrophic cardiomyopathy[10]. This results in prolonging QTc and action potential duration (APD).

2. Hypertension:

Hypertension has been known to be reciprocally correlated to CKD and its progression. This prompts cardiac muscle and autonomic nervous system modulation that eventually leads to QTc prolongation[11].

3. Uremic Toxins:

The water-soluble urea, creatinine, and phosphorus are collectively placed under the definition of 'uremic toxins '[12]. Their accumulation due to renal impairment results in oxidative stress and heart inflammation, which can contribute to myocardial electrophysiological disruption, fibrosis, and hypertrophy[13,14].

4. Electrolyte Disturbances:

Electrolyte imbalance, particularly in hyperkalemia and hypomagnesemia, leads to QTc prolongation and TWA. Although QT commonly shortens with hyperkalemia, some studies imply that prolongation of QT occurs just as much[15]. Hypomagnesemia causes failure of potassium influx by the impairment of the sodium-potassium ATPase pump's functionality, prolonging the cardiac action potential[16].

5. Medication Use:

There are plenty of well-documented QT-prolonging medications that can potentially cause QT prolongations. Beta-blockers, a chronic medication in this patient, have been observed to cause QT prolongation at slower heart rates[17]. Bradycardia-induced QT prolongation can be explained by the inverse relationship shared between the QT interval and heart rate (i.e., as heart rate increases, the QT interval tends to decrease, and vice versa). The QT interval is often corrected (QTc interval) for the current heart rate to account for the variation and accurately assess potential arrhythmic risk. It is valuable to note that the presence of a QTc greater than 500, TWA, and bradycardia increases the risk of torsades de pointes (a potentially fatal polymorphic arrhythmia), which beckons the need for close monitoring and management[18,19].

6. Genetic Factors:

There are 17 genes reported to cause Long QT syndrome. 3/17 genes (KCNQ1, KCNH2, SCN5A) were classified as having definitive LQTS genetic evidence[20]. Loss-of-function mutations in KCNQ1 and KCNH2 affect the slow delayed rectifier current and rapid delayed rectifier current, respectively. In contrast, a gain-of-function mutation in SCN5A affects the cardiac sodium channel responsible for the inward sodium current during the initial phase of the cardiac action potential. All of these mutations predispose the ventricular myocytes to early or delayed afterdepolarizations, which can lead to a potentially dangerous cardiac arrhythmia torsades de pointes[21]. The presence of genetic LQTS mutations can further complicate the clinical picture of a CKD patient, who are already highly liable to cardiovascular instabilities by electrolyte imbalances (primarily hyperkalemia in this case), uremic toxins, existing comorbidities (primarily hypertension and diabetes in this case), and medication sensitivity. Therefore, Genetic screening could help identify high-risk CKD patients.

Macroscopic TWA with QT prolongation

Macroscopic TWA has been reported to precede QT prolongation and signal acute ventricular arrhythmias, usually in the presence of electrolyte disturbances due to comorbid conditions[22,23,24]. TWA may be directly related to the risk factors navigated in this case as plausibly QTc prolonging. Although the mechanism of TWA has not been elucidated, the spatiotemporal dispersion of repolarization through fluctuations in APD restitution and impaired calcium cycling is frequently hypothesized[3,4].

To treat the multifactorial causes of QT interval prolongation and TWA, it is imperative to have them properly diagnosed. This can be achieved by careful and comprehensive medication review and assessing the patient's chronic illnesses, electrolyte levels, and uremic toxin levels. The patient's QT interval normalized after the initiation of hemodialysis. Potassium levels went from 5.8 to 4.3 mmol/L, and his Phosphorus of 1.56 mmol/L was corrected to 1.08 mmol/L. Before undergoing dialysis, his electrolyte disturbances were acutely managed using medication, including magnesium sulfate, kayexalate, lactulose solution, and insulin HR, which helped lower the QT interval and gradually resolve the TWA. This emphasizes the critical importance of involving a multidisciplinary team of nephrologists, cardiologists, and other healthcare professionals to better assess and manage a CKD patient with cardiac electrical instability.

The literature on the mechanisms underlying TWA and QT prolongation in CKD patients is limited, and more research must be conducted to understand better the relationship as well as develop strategies to reduce the overall risk of ventricular arrhythmias and sudden cardiac death in this population. This case calls for the integration of a timely and patient-tailored approach in the identification and testing of anticipated risk factors and comorbidities to deescalate cardiac electrophysiological disturbances in the form of QT prolongation, TWA, and atrial fibrillation. Dialysis initiation as a mainstay therapy in CKD patients with QT prolongation and TWA has been effective, highlighting the importance of considering it early in management. Furthermore, depleted electrolytes should be appropriately replenished, including administering magnesium sulfate to tackle TWA with prolonged QT interval.

CONCLUSION

TWA, characterized by beat-to-beat variations in T-wave morphology and amplitude on an ECG, has emerged as a robust marker for heightened risk of ventricular arrhythmias and SCD. Concomitantly, QT interval prolongation, indicative of extended ventricular repolarization, also portends an increased propensity for ventricular tachyarrhythmias. The intricate interplay of variables culminating in electrical instability in patients with advanced CKD is multifaceted and warrants further scientific inquiry to elucidate the underlying pathophysiological mechanisms.

This case underscores the imperative for a timely and personalized approach in identifying and addressing anticipated risk factors and comorbidities to mitigate cardiac electrophysiological perturbations manifesting as QT prolongation, TWA, and AF. The initiation of dialysis as a cornerstone therapy in CKD patients exhibiting QT prolongation and TWA has demonstrated efficacy, underscoring the importance of its early consideration in the management algorithm. Moreover, judicious replenishment of depleted electrolytes, including administering magnesium sulfate to address TWA in prolonged QT interval, is paramount.

The paucity of literature elucidating the precise mechanisms underpinning TWA and QT prolongation in CKD patients underscores the urgent need for further research to delineate the complex interrelationships better and develop targeted strategies to attenuate the overall risk of ventricular arrhythmias and sudden cardiac death in this vulnerable population. This case serves as a clarion call for integrating a multidisciplinary, patient-centric approach to optimize outcomes in CKD patients with cardiac electrical instability.

ETHICAL APPROVAL

The study was approved by the King Abdullah International Medical Research Center (KAIMRC) NRA24/003/5.

COMPETING INTERESTS

The authors have declared that no competing interests exist

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