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New-Onset Atrial Fibrillation After Exenatide Injection: Coincidence or Consequence?

CASE REPORT
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ABSTRACT

The glucagon-like peptide 1 receptor agonists, together with sodium-glucose cotransporter-2 inhibitors, are antidiabetic drugs known for their beneficial effects on the cardiovascular system; many phase 3 trials also support this conclusion. However, it can be thought that they may cause an increase in the risk of tachyarrhythmia due to the stimulation of their receptors in the sympathetic nervous system and sinoatrial cells. We report a case of a 71-year-old woman with no history of arrhythmia who presented with new-onset atrial fibrillation after an exenatide injection during clinical follow-up.

Keywords: Atrial fibrillation, exenatide, GLP-1 RA, triggered arrhythmia

Introduction

Type 2 diabetes mellitus (T2DM) is known to be an independent risk factor for atrial fibrillation (AF) and is associated with increased hospitalization, mortality, and poor quality of life. The glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are drugs widely used in the treatment of T2DM due to their incretin-mimetic effects. The GLP-1 RAs have also been shown to have many beneficial long-term cardiovascular effects. On the other hand, their use is associated with increased heart rate. The mechanism of increased heart rate associated with this class of agents is not fully understood, but it has been suggested that it may be due to the direct stimulation of sinus cells.[1] Furthermore, it is believed that these agents may affect the development of atrial arrhythmias through direct and indirect effects.

Case Presentation

A 71-year-old female with a medical history of T2DM (diagnosed 11 years ago), hypertension, gout, obesity, essential tremor, and chronic kidney failure presented with fluctuating blood glucose levels ranging from 80 to 200 mg/dL in fasting and from 200 to 250 mg/dL postprandial at home. The patient's current medication regimen included linagliptin 5 mg once daily, propranolol 40 mg once daily, amlodipine 10 mg once daily, and pantoprazole 40 mg once daily. During the outpatient evaluation, the patient was found to have mild diabetic neuropathy and stage 1 diabetic nephropathy. Past invasive coronary angiography, performed 2 years ago due to dyspnea, revealed nonobstructive coronary artery disease with mixed plaque causing 30%-40% stenosis in the mid-level of the left anterior descending artery. The patient exhibited clinical symptoms suggestive of orthostatic hypotension, sinus tachycardia in resting electrocardiography (ECG), grade 1 diastolic dysfunction, and mild myocardial hypertrophy in the left ventricle according to detailed transthoracic echocardiography (Figure 1). Due to these cardiovascular findings, elective Holter ECG monitoring was planned to evaluate cardiac autonomic neuropathy thoroughly. As glycemic control with oral antidiabetic agents proved insufficient and the patient's body mass index was above 35 kg/m^2, it was decided to initiate short-acting exenatide, a GLP-1 RA while discontinuing the dipeptidyl peptidase 4 (DPP-4) inhibitor (linagliptin). Within a brief interval of approximately 2 hours post exenatide administration, the patient exhibited nausea, vomiting, and palpitation symptoms. Notably, during the palpitation episode, the patient's ECG indicated the onset of AF accompanied by an elevated ventricular response (Figure 2). Exenatide treatment was promptly ceased, and the patient's previous propranolol dose for essential tremor was increased from 2 × 20 mg to 3 × 40 mg daily. Anticoagulant therapy was initiated based on the patient's congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA

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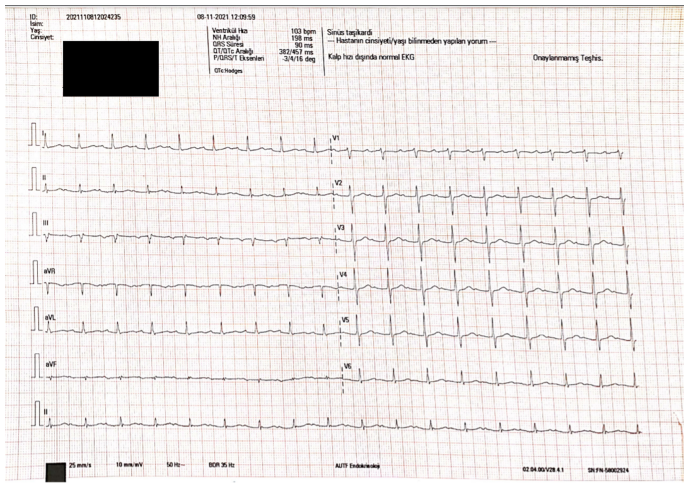

Figure 1. Basal electrocardiography of our patient after hospitalization: a first-degree atrioventricular block in sinus rhythm (the duration from the beginning of the P wave to the beginning of the R wave: 280 ms).

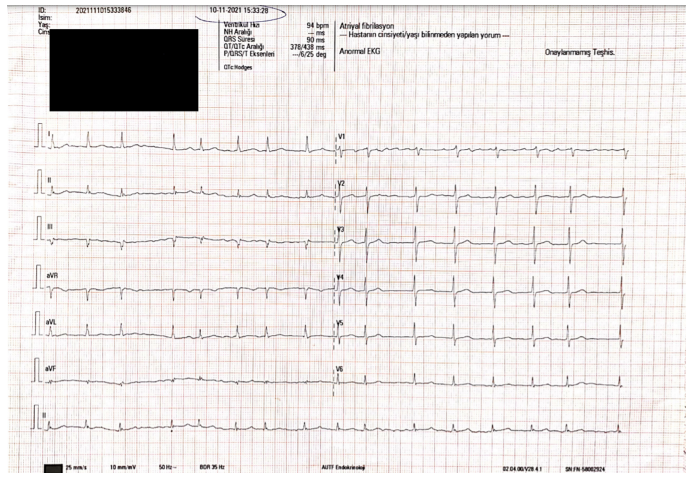

Figure 2. Atrial fibrillation was observed in the electrocardiography taken due to palpitation complaints of the patient after exenatide injection.

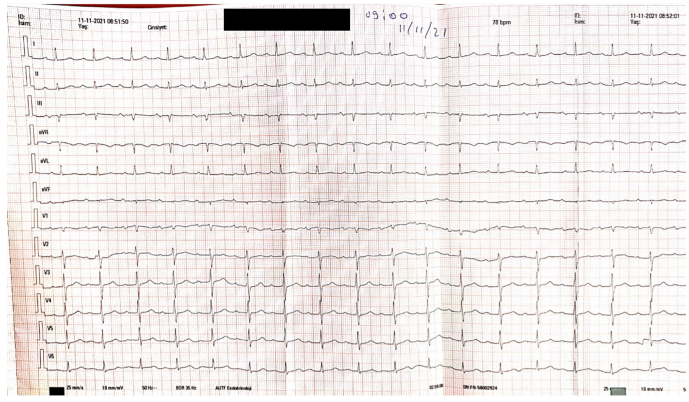

Figure 3. The patient's electrocardiography recorded the next morning after stopping exenatide showed a spontaneous transition to sinus rhythm.

or thromboembolism, vascular disease, age, sex category (CHA2DS2-VASc) score of 4. During follow-up, renal function deterioration was observed, and creatinine level, which was 1.12 mg/dL at hospitalization, increased to 1.5 mg/dL. Intravenous hydration was started considering prerenal acute kidney injury due to vomiting. No electrolyte imbalances, metabolic abnormality (including hypoglycemia), acidosis, hypoxia, or hypercarbia that could trigger AF was detected, and thyroid function tests were normal.

The following day, the patient's physical examination revealed regular pulses and the ECG showed a spontaneous return to sinus rhythm (Figure 3). Renal function recovered within 72 hours and returned to baseline levels. Metformin 2 × 500 mg was introduced for glycemic control with a thorough explanation of potential side effects. Atorvastatin 10 mg once daily was prescribed, considering the patient's low-density lipoprotein cholesterol value of 125 mg/dL. The oral anticoagulant treatment for triggered AF was adjusted with apixaban 5 mg twice daily until the follow-up 3 months later; therefore, acetylsalicylic acid was not added to the treatment due to the risk of bleeding in stable coronary artery disease. After 3 months, the patient was referred to the cardiology outpatient clinic for rhythm control evaluation. Informed consent was obtained from the patient before writing this case report.

MAIN POINTS

- Triggered atrial fibrillation refers to an arrhythmic condition that occurs as a result of autonomic alterations due to changes in the hemodynamic state or different drug effects.
- Long-term effects, the glucagon-like peptide 1 receptor agonists are known to reduce the frequency of ventricular arrhythmias, but controversial results have been reported regarding atrial arrhythmias.
- The glucagon-like peptide 1 receptor agonists may cause atrial arrhythmias through their receptors in the heart's sinoatrial node and autonomic nervous system cells. Detailed experiments are needed to understand the clinical significance of this effect.

Discussion

Drug-induced paroxysmal AF refers to the AF group that occurs as a result of acute exposure, independent of the presence of risk factors for AF. Mechanisms such as alterations in autonomic tone and exaggerated vagal and sympathetic stimulation have been introduced to explain this clinical picture.[2]

GLP-1 receptors are distributed across the autonomic nervous system, heart, pancreas, and gut. While gene expression is present in all cells forming the cardiac cavity, the receptors specifically located on the sinoatrial node are the ones that exhibit notable physiological effects. Stimulation of GLP-1 receptors in the autonomic nervous system has been demonstrated to increase sympathetic nervous system activity and decrease parasympathetic nervous system activity.[3,4] Additionally, GLP-1 RAs have been found to directly cause a collective increase in heart rate via atrial GLP receptors. A study comparing slow-release and short-acting exenatide and liraglutide formulations indicated a more pronounced effect of increasing heart rate in long-acting GLP-1 RAs.[5] However, there is currently a lack of strong evidence establishing a clear link between GLP-1 RAs and the initiation of AF attacks. While a placebo-controlled study with albiglutide

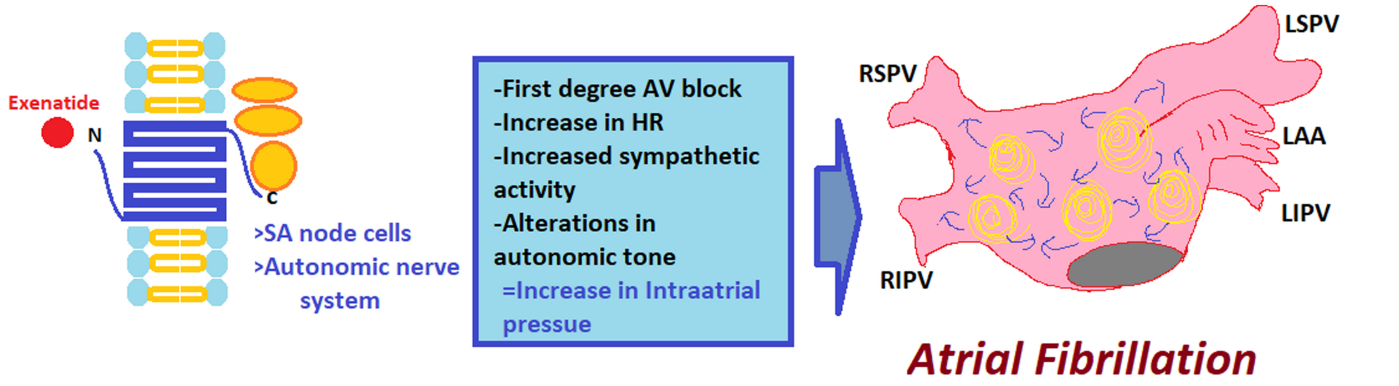

Figure 4. Possible responsible mechanisms suspected of triggered atrial fibrillation due to exenatide in our case. AV, atrioventricular; HR, heart rate; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SA, sinoatrial.

reported a statistically significant increase in AF risk,[6,7] there has been no reported case demonstrating triggered AF with exenatide yet. Another study investigating the cardiovascular outcomes of exenatide showed that AF developed in 4.4% of patients during follow-up. However, this percentage did not appear significantly different from the placebo group.[8] Upon meticulous examination of the data, it is observed that the exenatide arm had a lower rate of individuals with long-term T2DM and those above 75 years old compared to the placebo arm. This difference in demographics suggests that diabetes and age-related atrial myopathy in the study patients may have influenced the seemingly unremarkable AF rate triggered by the effect of exenatide. In a recent prospective cohort study comparing GLP-1 RAs, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and DPP-4 inhibitors, SGLT2 inhibitors were found to significantly reduce atrial arrhythmias compared to the other 2 drug groups. This finding supports the notion that GLP-1 RAs may not be superior to DPP-4 inhibitors regarding their antiarrhythmic effects.[9]

In our case, it can be thought that drug-related nausea and vomiting played a role in developing rhythm disorder in our patient by increasing vagal tone, as many drugs can. However, since the drug-related direct effects we suggested cannot be excluded, it can be hypothetically assumed that exenatide is a trigger for AF. The development of AF within 2 hours after exenatide injection prompted us to consider its potential role in triggering the arrhythmia. Exenatide's half-life of approximately 2.5 hours implies that its effects may persist for up to 10 hours, as typically, 4 half-lives are needed for negligible circulating amounts. The spontaneous return to sinus rhythm within 24 hours after discontinuing exenatide further supports this hypothesis. We postulate that exenatide may influence heart rate and autonomic tone fluctuations, along with the presence of a first-degree atrioventricular (AV) block observed in the basal ECG of our patient, potentially leading to an increase in intra-atrial pressure. First-degree AV block can impair left ventricle (LV) diastolic filling time, particularly in individuals with marked duration from the beginning of the *P* wave to the beginning of the r wave (PR) prolongation. As a result of PR prolongation, atrial contraction during periods of not low LV diastolic pressure could cause inadequate LV filling and diastolic mitral regurgitation, ultimately leading to chronic elevations in left atrial pressure and adverse remodeling. A similar pathophysiological scenario may occur in cases with a chronically high heart rate or in the presence of a triggering factor that acutely increases heart rate and/or sympathetic activity, even with mild PR prolongation.[10] Elevated left intra-atrial pressure may contribute to an increase in the rate and organization of depolarization waves originating from cells with automaticity in the pulmonary vein, which has been implicated in the pathogenesis of AF (Figure 4).[11] In our specific case, these proposed mechanisms may have played a crucial role in developing AF following exenatide administration. On the other hand, because a patient with a high CHA2DS2-VASc score may already have atrial myopathy, it is challenging to exclude incidental AF independent of exenatide injection as a natural process. Another limitation that prevented us from supporting our argument was that we did not try the drug again in this patient.

Beyond all these arguments, there are studies showing that exenatide and other GLP-1 RAs have protective effects, primarily on ventricular arrhythmogenesis in the long term, and the possible adverse effects we mentioned may be acute and temporary.[12,13]

Current clinical trials lack conclusive evidence regarding exenatide and the potential risk of AF. Based on the scientific data discussed here, it can be hypothetically stated that exenatide affects the development of atrial arrhythmia. More research is needed to assess the risk of arrhythmias with exenatide use.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflict of interest to declare.

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