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CASE REPORT

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Variant angina associated with a CGRP receptor antagonist: a case report

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Abstract

Background Calcitonin gene-related peptide (CGRP) plays a pivotal role in migraine pathophysiology, and CGRP receptor antagonists are increasingly used for acute and preventive treatment. While considered to have minimal cardiovascular risk, real-world safety data remain limited, particularly in patients with cardiovascular comorbidities. We report a rare case of variant angina associated with atogepant, a novel oral CGRP receptor antagonist.

Case presentation A 57-year-old woman presented with new-onset, paroxysmal chest pain over three days, described as a squeezing sensation with diaphoresis, typically occurring during early morning hours and relieved by sublingual nitroglycerin. She had a history of hypertension and IgA nephropathy and had been using zolmitriptan for chronic migraine for several years. Atogepant 60 mg once daily was initiated four days prior to reduce triptan use. On symptom onset, troponin I was mildly elevated but normalized by admission. Coronary angiography revealed no fixed stenosis or thrombosis. Given the clear clinical presentation, further spasm provocation testing was not performed, and variant angina was diagnosed. As no other causes of coronary vasospasm were identified, atogepant was discontinued, and diltiazem with a long-acting nitrate was prescribed. She remained symptom-free during follow-up.

Conclusions This case suggests that atogepant may be associated with coronary vasospasm in patients with cardiovascular risk factors. Given CGRP's role as a potent vasodilator, its blockade may predispose to vasospasm in vulnerable individuals. Caution and close monitoring are warranted when prescribing CGRP receptor antagonists, particularly in those with cardiovascular comorbidities.

Keywords CGRP receptor antagonist, Atogepant, Gepants, Migraine, Variant angina, Coronary vasospasm

Background

Calcitonin gene-related peptide (CGRP) has been identified as a pivotal factor in the pathophysiology of migraine [1]. Blocking CGRP has emerged as a therapeutic strategy for both acute migraine attacks and migraine prevention [2, 3]. The recent approval of oral formulations (gepants) is expected to further expand the use of CGRP receptor antagonists. Atogepant is a novel oral CGRP receptor antagonist approved for the prevention of both episodic and chronic migraine, with approved dosing regimens of 10 mg, 30 mg, or 60 mg once daily [4]. Unlike first-generation gepants, it overcomes earlier concerns regarding hepatotoxicity [5].

Traditionally, triptans and ergot derivatives have been used for acute migraine treatment, but their potential to induce coronary vasospasm necessitates caution in patients with cardiovascular diseases [6]. While CGRP receptor antagonists are considered to carry minimal cardiovascular risk compared to triptans or ergot

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derivatives, real-world data on their safety in patients with cardiovascular comorbidities remain limited [5].

Variant angina is caused by coronary vasospasm, and several medications have been identified as potential triggers. To date, it has not been specifically reported whether oral CGRP receptor antagonists can directly induce this condition. We report a rare case of variant angina associated with atogepant, a novel oral CGRP receptor antagonist, highlighting the need for further investigation into its cardiovascular safety for more tailored patient populations.

Case presentation

A 57-year-old woman was referred from a primary clinic due to new-onset paroxysmal chest pain that began three days ago. The pain, described as a squeezing sensation with diaphoresis, occurred primarily during early morning sleep and was unrelated to exertion, and had never been experienced by the patient before. Episodes were relieved within minutes with sublingual nitroglycerin but could persist up to an hour without treatment. The patient had a 10-year history of hypertension and IgA nephropathy with chronic kidney disease stage 3, managed with losartan 25 mg and dapagliflozin 10 mg once daily, with stable renal function. For chronic migraine management, she had been using zolmitriptan 2.5 mg as needed, up to 1–2 times daily, for several years, as prescribed by her neurologist. To reduce her reliance on zolmitriptan, the neurologist initiated atogepant 60 mg once daily in the evening, beginning four days earlier. She reported adherence to the new regimen and denied taking any additional zolmitriptan during that period. She had no history of alcohol consumption or smoking. She had experienced emotional stress related to a family health issue for the past year, but this stress had not worsened recently.

On physical examination, her blood pressure was 130/74 mmHg, heart rate 70 bpm, and cardiac examination was unremarkable. Chest X-ray showed no infiltrates, edema, or cardiomegaly, and the initial electrocardiogram revealed normal sinus rhythm without ST-segment changes. Two days prior, high-sensitivity troponin I at the primary clinic was mildly elevated at 33.6 pg/mL (reference: < 10.4 pg/mL). However, repeat testing upon admission to our institution showed a decrease to 4.2 pg/mL, within the normal range (Table 1). Echocardiography revealed no abnormalities in cardiac function or structure.

Table 1 Laboratory examination

	At presentation	At admission	Reference range
WBC (x 10^3/μL)	7.44	8.11	4.00 ~ 10.00
Hemoglobin (g/dL)	13.2	13.6	12.0 ~ 16.0
BUN (mg/dL)	29	30	6 ~ 20
Creatinine (mg/dL)	1.57	1.62	0.50 ~ 0.90
CK (U/L)	72	56	26 ~ 192
CK-MB (ng/mL)	0.92	0.7	0.5 ~ 5.0
High-sensitivity troponin I (pg/mL)	33.6	4.2	< 10.4

*WBC = white blood cell; BUN = blood urea nitrogen; CK = creatin kinase; CK-MB = creatin kinase myocardial band

Given the presence of unstable angina with changes in cardiac markers, coronary angiography was performed to rule out atherosclerotic coronary disease. Coronary angiography revealed no evidence of fixed stenosis or thrombosis (Fig. 1). Due to the clarity of the patient's clinical presentation, the procedure was concluded without further spasm provocation testing, and the patient was diagnosed with variant angina. As no other causes of coronary vasospasm were identified, the patient was advised to discontinue atogepant and was prescribed diltiazem and a long-acting nitrate. During a two-week follow-up period, she remained symptom-free.

Discussion and conclusions

In this case report, the patient presented with transient elevation of cardiac biomarkers but no evidence of atherosclerotic disease on coronary angiography. Her symptoms responded well to nitrates and calcium channel blockers. Although coronary vasospasm was not confirmed by provocation testing, the favorable response to nitroglycerin and the typical occurrence of chest pain during early morning hours strongly supported the diagnosis of variant angina. While troponin levels may occasionally be nonspecifically elevated in patients with chronic kidney disease due to reduced clearance, dynamic changes—particularly when accompanied by typical clinical features, as in this case—are less likely to reflect a non-cardiac cause and warrant careful clinical suspicion.

Variant angina is characterized by chest pain at rest due to coronary vasospasm. The mechanism of vasospasm involves vascular smooth muscle hyperreactivity and autonomic nervous system dysfunction, with endothelial dysfunction further contributing to its occurrence [7]. Coronary vasospasm is often triggered by alcohol consumption, and migraine medications such as triptans or ergot derivatives have been reported to induce vasoconstriction [8, 9]. In this patient, there was no history of alcohol use. Despite long-term triptan use, she had never experienced anginal symptoms, and notably, she had not taken any zolmitriptan since initiating atogepant four days earlier. Thus, the recently initiated CGRP receptor antagonist was considered the most plausible trigger of vasospasm.

CGRP is a neuropeptide released from perivascular nerve fibers following trigeminal nerve activation and acts as a potent vasodilator within the trigeminovascular

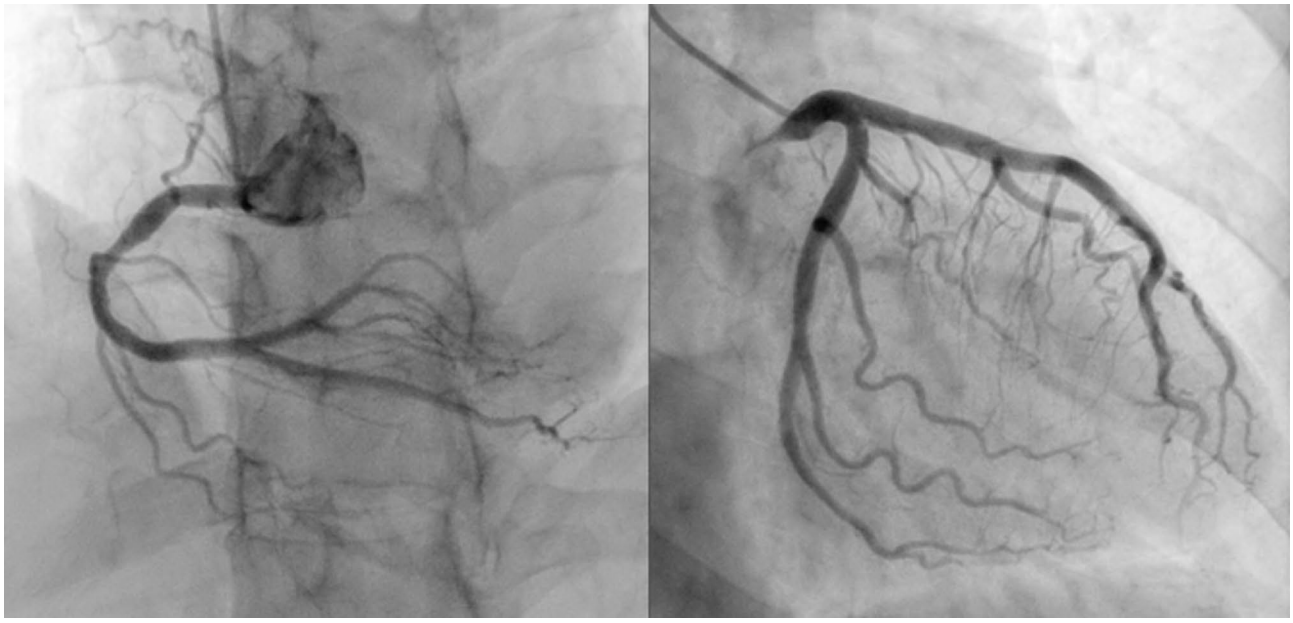

Fig. 1 Coronary angiography: no evidence of fixed stenosis or thrombosis

system [1]. The signaling pathways promoted by CGRP have been identified as a key component of migraine pathophysiology, leading to the development of various therapies targeting CGRP and its receptor [10]. Currently approved CGRP receptor antagonists include monoclonal antibodies targeting CGRP or its receptor (eptinezumab, erenumab, fremanezumab, and galcanezumab) and the more recently approved oral CGRP receptor antagonists, known as gepants (ubrogepant, rimegepant, and atogepant) [3, 11].

Interestingly, CGRP receptors are present not only in the central and peripheral nervous systems but also in the cardiovascular system, including coronary arteries [12]. CGRP, a potent vasodilator, plays a similar role in coronary arteries and has been shown to exhibit increased expression in myocardial infarction [13, 14]. Its protective role against vasospasm has also been demonstrated in animal models [15]. Furthermore, the presence of mRNA encoding the components of the CGRP1 receptor has been confirmed in human coronary arteries, and inhibition of this receptor was shown to attenuate vasorelaxation [16]. In this context, blocking CGRP signaling may potentially induce or exacerbate coronary vasospasm. Notably, there have also been case reports of myocardial infarction occurring after the administration of CGRP receptor antagonists [17].

We acknowledge that the diagnosis was made clinically and by exclusion, and that other contributing factors, including long-term triptan use, cannot be entirely ruled out. Cardiovascular safety of CGRP receptor antagonists has been demonstrated in randomized controlled trials; however, it is important to note that these studies largely excluded patients with preexisting cardiovascular disease, including those with a history of myocardial infarction, coronary vasospasm, or excessive triptan use [18–20]. In the present case, the patient had used triptans regularly for years without any episodes of chest pain, yet developed typical symptoms of variant angina one day after initiating atogepant. While causality cannot be definitively established, it is plausible that the patient's underlying condition—IgA nephropathy with chronic kidney disease, which is associated with endothelial dysfunction [21].—and prior triptan exposure may have contributed to increased susceptibility to atogepant-associated coronary vasospasm.

In addition, potential pharmacokinetic factors should be considered. Atogepant is primarily metabolized via cytochrome P450 3A4 (CYP3A4), and although the patient was taking losartan and dapagliflozin, neither is known to significantly affect CYP3A4 activity. Therefore, a clinically relevant drug–drug interaction was unlikely in this case.

Our clinical case suggests that CGRP receptor antagonists may require caution regarding cardiovascular adverse events, such as coronary vasospasm, in patient populations excluded from large-scale studies—those with cardiovascular comorbidities or excessive triptan use. Further data are needed to confirm the risk of coronary vasospasm in more specific patient populations and to assess the potential class effect of CGRP receptor inhibitors. Additionally, careful patient monitoring is essential when atogepant and triptans are administered concurrently.

Abbreviations
CGRP Calcitonin gene-related peptide

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Author contributions
H. Jeon was responsible for the case description, initial manuscript drafting and literature review. J.M. Cho contributed to manuscript revision. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent to publication
The authors confirm that written consent for submission and publication of this case report has been obtained from the patient in line with COPE guidelines.

Competing interests
The authors declare no competing interests.

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