ESC European Society of Cardiology

European Heart Journal - Case Reports (2024) **8**, ytae249
https://doi.org/10.1093/ehjcr/ytae249

CASE REPORT
Cardiovascular imaging

Bilateral isolated coronary ostial stenosis in a middle-aged premenopausal woman with vasospastic angina: a case report

Koji Takahashi [1,2]*, Akihiro Kodama[3], Shigeki Uemura[2], and Takafumi Okura[2]

[1]Department of Community Emergency Medicine, Ehime University Graduate School of Medicine, 454 Shitsukawa, Toon, Ehime 791-0295, Japan; [2]Department of Cardiology, Yawatahama City General Hospital, 1-638 Ohira, Yawatahama, Ehime 796-8502, Japan; and [3]Department of Internal Medicine, Seiyo Municipal Hospital, 147-1 Nagaosa, Seiyo, Ehime 797-0029, Japan

Received 25 October 2023; revised 29 April 2024; accepted 13 May 2024; online publish-ahead-of-print 15 May 2024

Background Vasospastic angina (VSA) is uncommon in premenopausal women who have less chronic endothelial injury causing vascular remodelling, considered to play a primary role in the pathogenesis for coronary vasospasms. Furthermore, vasospasms rarely occur in the bilateral coronary ostia. Isolated coronary ostial stenosis (ICOS), which often causes severe effort angina and requires surgical intervention, is more commonly reported in middle-aged women, with causes including fibromuscular dysplasia (FMD) and large-vessel vasculitis. However, ICOS associated with VSA is extremely rare.

Case summary A 50-year-old premenopausal Japanese woman presented with a complaint of typical chest pain due to angina during light exertion daily in the early morning hours since 3 years. Coronary angiography (CAG) revealed bilateral mild-to-moderate ICOS in addition to multi-vessel spasms involving the bilateral coronary ostia confirmed by the vasospasm provocation test using intracoronary acetylcholine injection. Tests to determine the cause of ICOS did not identify FMD or any other disease. The angina attacks alleviated after calcium channel blocker (CCB) administration without intervention for bilateral ICOS for 24 years since the first presentation. Moreover, coronary computed tomography angiography (CTA) performed 24 years after the first presentation showed no ICOS.

Discussion In our patient with typical and frequent VSA symptoms, CAG revealed both mild-to-moderate ICOS and the vasospasms in the bilateral coronary ostia. Fibromuscular dysplasia or large-vessel vasculitis was ruled out as the causes of ICOS. Vasospastic angina rarely occurred after the prescription of CCB, and coronary CTA 24 years after the first presentation showed no ICOS. Bilateral ICOS in our patient might be VSA related.

Keywords Acetylcholine • Calcium channel blocker • Case report • Isolated coronary ostial stenosis • Premenopause • Vasospastic angina

ESC curriculum 3.1 Coronary artery disease • 3.4 Coronary angiography • 3.3 Chronic coronary syndrome

* Corresponding author. Tel: +81 894 22 3211, Fax: +81 894 24 2563, Email: michitokitatsumasa@gmail.com
Handling Editor: Edoardo Zancanaro
Peer-reviewers: Annagrazia Cecere; Sumit Sohal; Zaid Iskandar; Milanko Zoran Cankovic; Kashan Ali
Compliance Editor: Abdelsalam Bensaaud

Learning points

- If patients complain of typical angina that usually occurs at rest and during light exertion from midnight to early morning, vasospastic angina (VSA) should be considered, even in premenopausal women.
- In case of bilateral isolated coronary ostial stenosis (ICOS) detected on coronary angiography (CAG) or coronary computed tomography angiography, visual assessment of all vessels from the brain to the pelvis using imaging is recommended to investigate the involvement of fibromuscular dysplasia and large-vessel arteritis.
- Frequent VSA attacks occurring in the coronary ostium may lead to ICOS, and angina control by prescription of calcium channel blockers may improve ostial stenosis without revascularization.
- Intermediate isolated coronary artery stenosis that is not indicated for surgery on the basis of physiological evaluation requires careful follow-up with CAG or coronary computed tomography.

Introduction

Isolated coronary ostial stenosis (ICOS) with normal distal coronary arteries is considered rare.[1] Although atherosclerosis is considered the most likely cause of ICOS, other causes include fibromuscular dysplasia (FMD), syphilitic aortitis, Takayasu arteritis, and mediastinal irradiation.[2] Isolated coronary ostial stenosis is more commonly reported in middle-aged women with few typical cardiovascular risk factors, usually before menopause.[1–3] In general, patients with ICOS present with severe effort angina with a short time from onset to hospital visit.[1,3] Although the long-term angiographic characteristics of affected patients have not been fully studied, coronary ostial stenosis shows significant improvement in some cases.[2]

Coronary artery spasm (CAS) is one mechanism leading to myocardial ischaemia; it involves a mismatch between blood supply and myocardial oxygen demand in the setting of non-obstructive coronary arteries.[4] Coronary artery spasm contributes to the pathogeneses of variant angina and acute coronary syndrome. Vasospastic angina (VSA) attacks usually occur at rest and during light exertion from midnight to early morning. Vasospastic angina is uncommon in premenopausal women who have less chronic endothelial injury causing vascular remodelling, considered to play a primary role in the pathogenesis for CAS.[5,6] Vasospasms in the bilateral coronary ostia induced by an intracoronary injection of ergonovine or acetylcholine as a provocative stimulus are extremely rare.[5] Moreover, there are few reports of ICOS associated with spasms in the coronary ostia.

Here, we describe a case involving a middle-aged premenopausal woman with acetylcholine-provoked multi-vessel spasms involving the ostia of the left (LCA) and right (RCA) coronary arteries and bilateral ICOS. In addition, we describe our course of investigations that led to the determination of the cause of ICOS in this case.

Summary figure

Timeline	Patient history and test results
3 years prior to admission	Anterior chest squeezing lasting 5 min, which radiated to the left axilla and was sometimes associated with diaphoresis, occurred every morning when the patient washed her face and brushed her teeth immediately after waking up.
1 month prior to admission	Anterior chest squeezing began to occur during the daytime, in addition to early in the morning.
Day 1 (at age 50 in 1999)	• The patient was admitted to the hospital. • The patient's vital signs were as follows: temperature, 37.0°C; pulse rate, 84 b.p.m.; systemic blood pressure, 130/84 mmHg; and respiratory rate, 16/min. • Physical examination findings were unremarkable. • Blood tests revealed normal lipid profile and glucose levels, and no inflammatory reaction. Serological test results for syphilis were negative. • Chest X-ray, electrocardiogram (ECG), and echocardiographic findings were also unremarkable. • The patient was suspected to have unstable angina mainly due to coronary vasospasm and was prescribed nisoldipine, isosorbide mononitrate, and aspirin. Chest pain attacks subsided.
Day 6	Nisoldipine was withdrawn without the recurrence of chest pain.
Day 7	Isosorbide mononitrate was withdrawn without the recurrence of chest pain.
Day 8	• Coronary angiography (CAG) was performed. • A control angiogram showed non-significant stenoses at the left coronary artery (LCA) and right coronary artery (RCA) ostia, with normal distal coronary arteries (ICOS). • A provocative test for coronary vasospasm (CAS) using an intracoronary injection of acetylcholine revealed multi-vessel spasm, including a bilateral ostia of the LCA and RCA, together with chest pain and ischaemic ECG changes. • Coronary angiography after an intracoronary injection of isosorbide dinitrate revealed intermediate stenosis at the ostia of the LCA and RCA.

Continued

Continued

Timeline	Patient history and test results
	• The patient was again prescribed nisoldipine and isosorbide mononitrate.
Day 9	Duplex ultrasonography of the carotid and renal arteries to determine the aetiology of ICOS showed no findings suggestive of fibromuscular dysplasia (FMD).
Day 10	The patient was discharged home.
Years 1–23	• The patient was prescribed only calcium channel blockers at another clinic and did not have typical CAS attacks. • During this time, CAG or coronary computed tomography angiography (CTA) was not performed.
Year 24 (at age 74 in 2023)	Coronary CTA revealed no luminal narrowing, including the ostia of the LCA and RCA. In addition, systemic CTA revealed no findings that suspected FMD or traces of post-inflammation in the aorta, such as Takayasu arteritis.

Case presentation

A 50-year-old premenopausal Japanese woman was admitted to our hospital with a 3-year history of anterior chest squeezing lasting 5 min that occurred every morning when she washed her face and brushed her teeth immediately after waking up. The squeezing radiated to the left axilla and was sometimes associated with diaphoresis. One month before admission, chest pain attacks began to occur during the day in addition to those occurring early in the morning. The patient had no history of tobacco, alcohol, or illicit drug consumption. Her medical history was unremarkable.

Her vital signs were as follows: temperature, 37.0°C; pulse rate, 84 b.p.m.; systemic blood pressure, 130/84 mmHg; and respiratory rate, 16/min. Physical examination findings were unremarkable. Blood tests revealed normal lipid profile and glucose levels and no inflammatory reaction. Serological test results for syphilis were negative. Chest radiography, electrocardiography, and echocardiography findings were also unremarkable.

Unstable angina, mainly due to CAS, was suspected, and nisoldipine (10 mg once daily), isosorbide mononitrate (20 mg twice daily), and aspirin (81 mg once daily) were prescribed. No angina attacks occurred after admission. Coronary angiography (CAG) was performed after nisoldipine and isosorbide mononitrate were discontinued. A control angiogram showed only non-significant stenoses in the bilateral coronary ostia. Therefore, a provocative test for CAS was performed with acetylcholine, as reported previously.[7–9] After an intracoronary injection of 20 μg acetylcholine into the LCA (*Figure 1A*), severe vasoconstriction, accompanied by the usual chest pain and ischaemic electrocardiogram (ECG) changes (*Figure 2*, left and middle), occurred in the entire LCA, including the ostium, with delayed contrast washout in the left anterior descending artery. When acetylcholine-provoked CAS in the LCA subsided after intracoronary isosorbide dinitrate (4 mg) injection, incremental doses of acetylcholine (20, 50, and 80 μg) were injected into the RCA. Finally, a severe vasoconstriction of some segments, including the ostium (*Figure 1B*), occurred with chest pain and ischaemic ECG changes (*Figure 2*, left and right). After intracoronary isosorbide dinitrate (4 mg) injection into the RCA, acetylcholine-provoked CAS subsided. Final angiography showed intermediate stenoses in the bilateral coronary ostia (*Figure 1C–F*).

The patient was diagnosed with multi-vessel CAS, and nisoldipine and isosorbide mononitrate were reinitiated. Duplex ultrasonography of the carotid and renal arteries to determine the aetiology of ICOS showed no findings suggestive of FMD. The patient's angina was considered secondary to CAS but not to ICOS. Although a physiological examination using a pressure wire to guide the decision for revascularization was not performed, the severity of the bilateral ICOS was considered low; thus, it was not indicated for surgery. Subsequently, the patient was prescribed calcium channel blockers (CCBs) at another clinic for 24 years since the first presentation, and the VSA attacks disappeared.

At 74 years of age, 24 years after the first presentation, the patient presented to our hospital with atypical chest pain. Coronary computed tomography angiography (CTA) showed no luminal narrowing throughout the epicardial coronary arteries, including the bilateral ostia (*Figure 3*). Systemic CTA showed no involvement of the major aortic branches (*Figure 4*).

Discussion

If invasive CAG reveals ICOS, its causes should be investigated in all patients except those with uncontrollable ischaemic symptoms and haemodynamic instability, which necessitate emergent intervention. However, catheter-induced spasm in the coronary artery ostia should be ruled out first via repeated intracoronary nitrate administration.[10,11] If catheter-induced spasms are still suspected, intravascular ultrasound (IVUS) and coronary CTA are useful diagnostic tools for their confirmation.

The ostia of the coronary arteries lie within the aortic wall,[12] making them prone to organic changes, including ICOS, by any diseases affecting the aorta, particularly atherosclerosis, FMD, Takayasu arteritis, syphilitic aortitis, and mediastinal irradiation.[2] While no established algorithm is available, ICOS is generally diagnosed based on clinical suspicion supported by imaging studies. In systemic non-atherosclerotic diseases, such as FMD and Takayasu arteritis, visual assessment of all vessels from the brain to the pelvis using imaging, particularly CTA, was recently recommended.[13] Computed tomography angiography may reveal extremely rare causes of ICOS.[14] Our patient was a premenopausal, middle-aged woman with no coronary risk factors at initial presentation, and atherosclerosis was an unlikely cause of bilateral ICOS. Resolution of the coronary ostial stenosis supports this idea.[2] Other causes of ICOS were ruled out by blood tests, including those for inflammatory reactions and serological tests for syphilis, and duplex ultrasonography of the carotid and renal arteries, leading us to consider CAS-related bilateral ICOS.

The Japanese population has a higher prevalence of CAS than do Western populations. In a study of ≥1000 Japanese patients with VSA, the patients' average age was 66 years; approximately a quarter was women, with even fewer premenopausal women. Multi-vessel spasm was documented in 32% patients, whereas left main trunk (LMT) spasm was not observed.[4,5] Coronary artery spasm involves hypercontraction based on hyperactivity of the Rho-kinase pathway in vascular smooth muscle cells, endothelial dysfunction, and inflammation of the vascular adventitia and perivascular adipose tissue.[15] Advancement of intracoronary imaging modalities has helped elucidate the pathophysiology of CAS through coronary artery wall observations, although the ostial lesions have not been investigated.[15] Particularly, the effectiveness of optical coherence tomography (OCT) for imaging the aorto-ostial lesions is limited, given the need for a bloodless field for adequate imaging. Intravascular ultrasound revealed that even angiographically normal coronary arteries have intimal thickening and mild atherosclerosis at spasm sites in patients

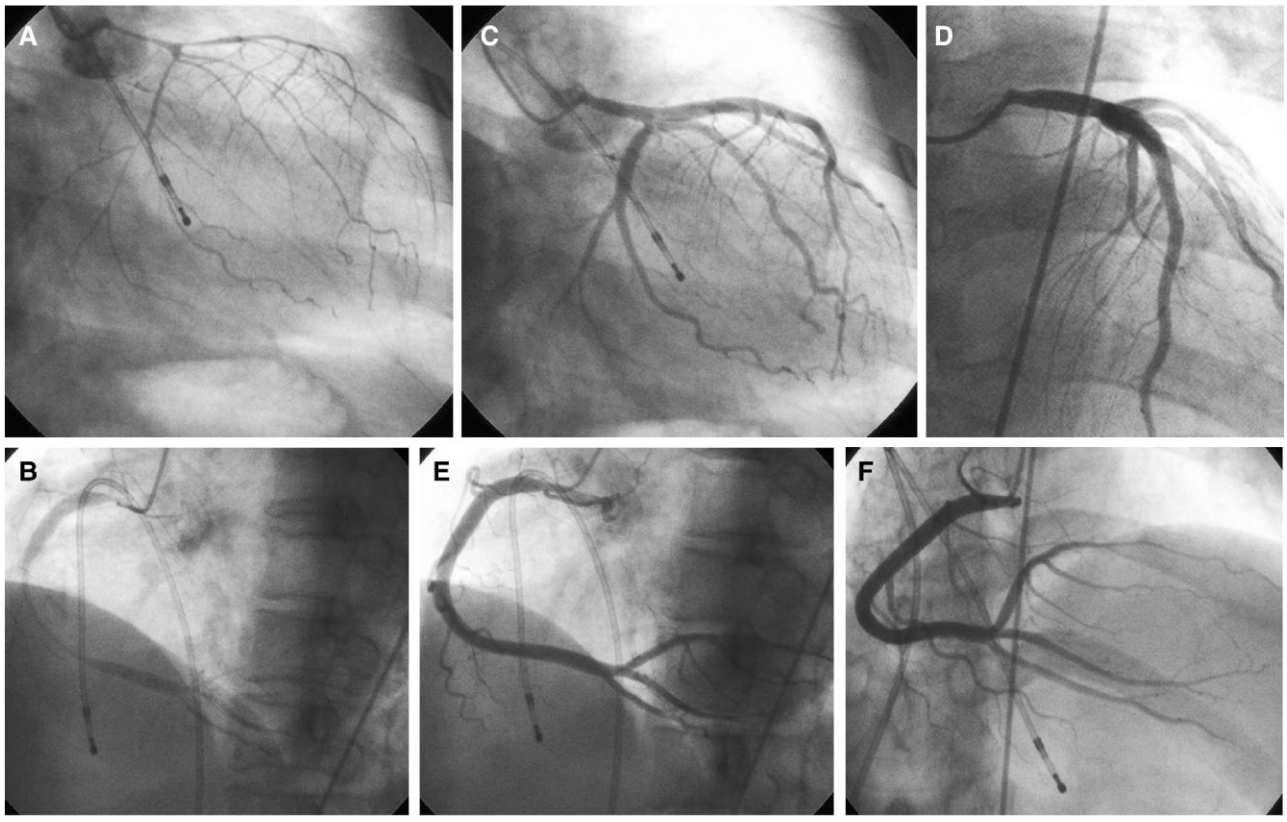

Figure 1 Coronary angiograms. (*A*) After an intracoronary injection of acetylcholine 20 μg into the left coronary artery, severe vasoconstriction occurs in the entire left coronary artery, including the ostium of the left coronary artery, with washout delay of the contrast in the left anterior descending artery. (*B*) After an intracoronary injection of acetylcholine 80 μg into the right coronary artery, severe focal vasoconstriction including in the ostium is induced. After an intracoronary injection of isosorbide dinitrate into the left coronary artery (*C* and *D*) and right coronary artery (*E* and *F*), 50–75% stenoses in the ostia of the left coronary artery and right coronary artery are shown, but the remaining coronary arteries are not stenotic.

with VSA.[15] Spasm sites also frequently show negative remodelling with a reduced diameter. Optical coherence tomography revealed organic lesions, such as layered plaque, intimal tears, thrombi, and coronary artery dissection, probably caused by CAS at more than half the spasm sites with no significant stenosis on CAG. During coronary spasm, the area and thickness of the tunica media have been reported to significantly increase due to hypercontraction.[15]

Coronary artery spasm occurs less often in the coronary ostia because of the morphologically specific structure that differs from the structure of other parts of the coronary arteries.[2] The ostia lie within the aortic wall, lack the adventitia, and form a funnel-shaped structure characterized by a longitudinal smooth muscle arrangement spreading out into an inner layer and a circular smooth muscle arrangement surrounding the outer layer. The ostia also have considerable elastic tissue, and the amount of elastic tissue reduces distally in the coronary tree.[12] However, an atherosclerotic plaque at the most proximal segment of the coronary arteries is accompanied by a marked atrophy of the tunica media, with a reduction in elastic and smooth muscle fibres.[16] In our patient with no coronary risk factors, angina attacks due to CAS occurred every day for 3 years, although a cyclic variation in endothelial function and the frequency of myocardial ischaemia are associated with oestrogen variations in premenopausal women with variant angina.[17] Moreover, multi-vessel spasms involving the bilateral coronary ostia were provoked by acetylcholine, although acetylcholine-provoked CAS does not always represent the spastic site during spontaneous angina attacks. Thus, we suspected that bilateral ICOS was caused by organic changes due to frequent CAS attacks in the bilateral coronary ostia, although no association between CAG images and histopathological or IVUS/OCT findings was confirmed. The obvious reason for the occurrence of organic stenosis only in the bilateral coronary ostia was unclear.

Patients with ICOS in the setting of acute coronary syndrome require emergent intervention for ICOS, such as coronary artery bypass grafting or percutaneous revascularization. In ICOS patients with chronic coronary syndrome, a physiology-guided treatment decision to perform revascularization is recommended.[1–3,11] In the case of our patient, coronary CTA performed 24 years after the first presentation did not show ICOS. Female sex and a low comorbidity of epicardial coronary artery stenosis correlate with the acetylcholine-provoked diffuse spasm pattern in patients with VSA. However, our patient had acetylcholine-provoked multi-vessel spasms with both focal and diffuse patterns, indicating a worse prognosis than that of diffuse CAS alone.[5] In contrast, the clinical features and prognosis of acetylcholine-provoked CAS are different when spasms occur at sites of significant atherosclerotic stenosis than when spasms occur elsewhere.[18] Although CAS often causes silent myocardial ischaemia,[6] we suspected that CAS attacks rarely occurred after the prescription of CCBs in our patient, with subsequent resolution of organic stenosis and disappearance of ICOS on coronary CTA performed 24 years after the first presentation.[19,20] Statins, which improve the prognosis of patients with VSA without significant organic stenosis, would be better administered to patients with severe multi-vessel spasm, such as our patient.[21]

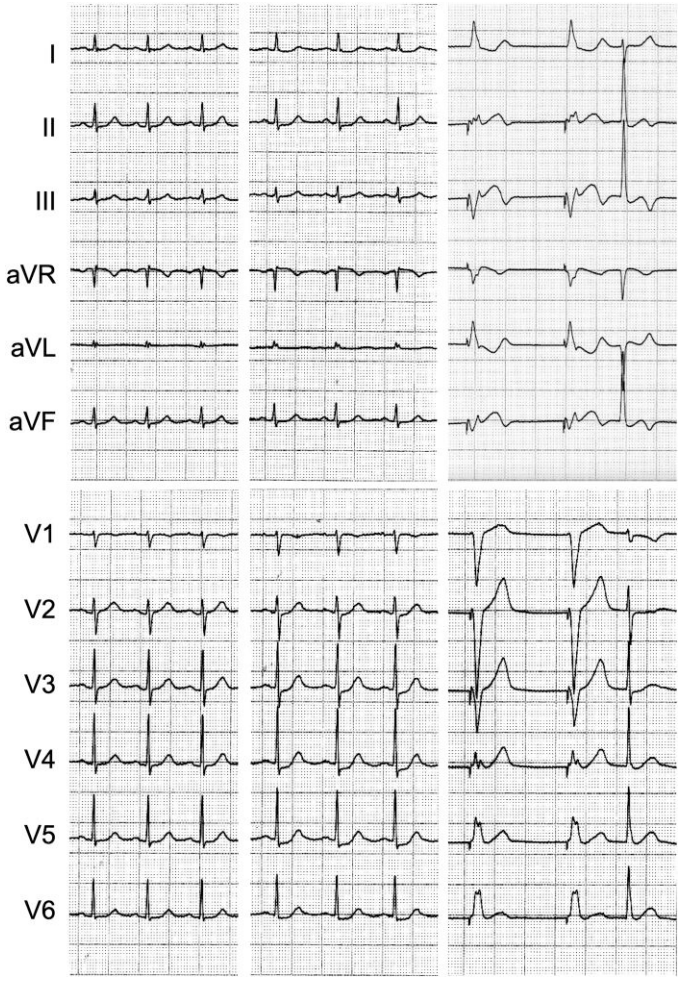

Figure 2 Electrocardiograms recorded during provocative testing for coronary vasospasm using an intracoronary injection of acetylcholine as the provocative stimulus. Baseline electrocardiogram is normal (left). During coronary vasospasm induced in the left coronary artery (middle), ST-segment elevation in Lead aVR, ST-segment depression in Leads I, II, aVL, and V3-6, and negative U waves in Leads V4 and V5 are shown. During coronary vasospasm induced in the right coronary artery (right), ST-segment elevation in Leads II, III, and aVF is observed concomitant with right ventricular pacing.

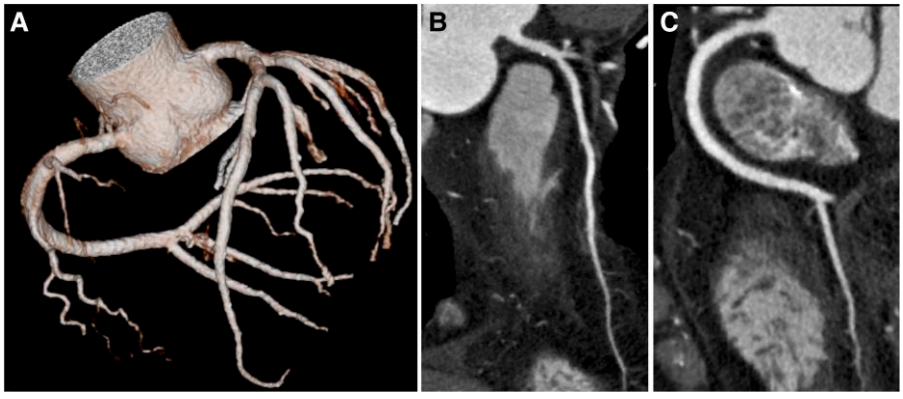

Figure 3 Coronary computed tomographic angiography. Three-dimensional volume-rendered image of the left and right coronary arteries (*A*) and curved multi-planar reconstruction images of the left main trunk to the left anterior descending coronary artery (*B*) and the right coronary artery (*C*) show no luminal narrowing.

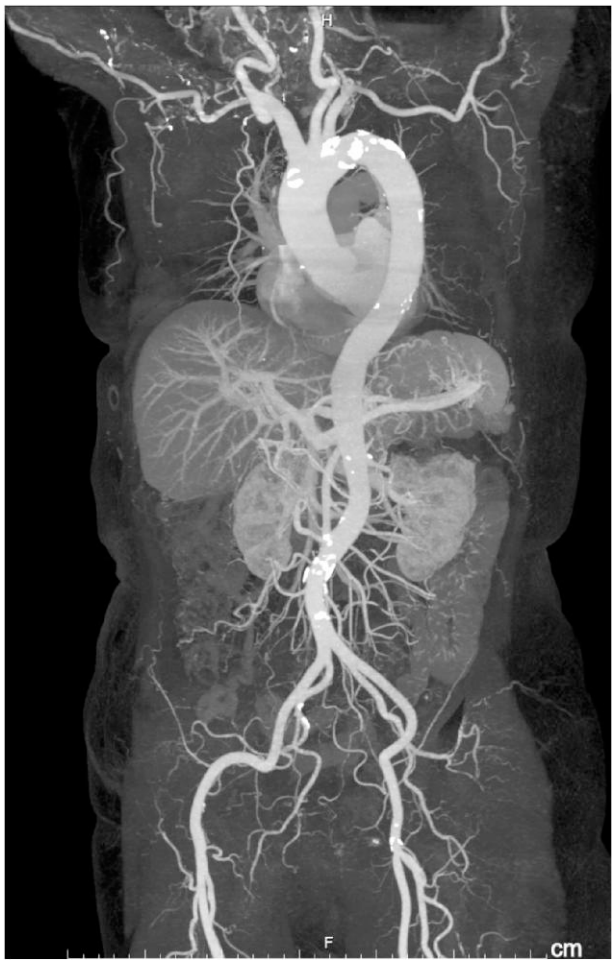

Figure 4 Systemic computed tomographic angiography. The maximum intensity projection image shows no focal stenosis/occlusion, dilation, or the 'S curve' as severe tortuosity at the aorta and its main branches due to well-known diseases leading to isolated coronary ostial stenosis, such as fibromuscular dysplasia and Takayasu arteritis, although buckling and mild calcification are present.

This case report had some limitations. First, the coronary ostia were not evaluated using IVUS/OCT and coronary CTA at the initial presentation in 1999; however, at that time, intracoronary imaging modalities were not widely available, even for percutaneous coronary intervention procedures.[22] The same was true for coronary CTA. Second, no physiology-guided treatment decision was made for ICOS with intermediate stenosis. The 2018 ESC/EACTS Guidelines on myocardial revascularization recommend the Class IA indication for physiological assessments to guide the revascularization of intermediate-grade stenosis, including LMT disease.[11] However, LMT disease was extremely rare in early validation studies. Finally, ICOS was not histopathologically confirmed because no surgical intervention was performed.

Conclusion

This case highlights bilateral ICOS that could be caused by suspected organic stenosis due to frequent CAS attacks in the bilateral coronary ostia. Thus, coronary artery vasospasms can be listed as one of the factors causing ICOS.

Lead author biography

Dr Koji Takahashi is a cardiologist at Yawatahama City General Hospital in Japan. He is also a lecturer at Ehime University Graduate School of Medicine in Japan. His research interests focus on systemic amyloidosis, particularly wild-type transthyretin amyloidosis.

Acknowledgements

The authors express their sincere thanks to Ms Yumie Hiraoka for her assistance with this study. They also thank Editage (www.editage.com) for the English language editing.

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

Data availability

The data supporting the findings of this case report are available within the article itself. Further anonymized data underlying this article will be shared upon reasonable request with the corresponding author.

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