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Case report

ST-segment elevation in V1–4 in takotsubo cardiomyopathy with ventricular septal perforation: A case report and literature review

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ABSTRACT

Background: Takotsubo cardiomyopathy (TCM) is a nonischemic cardiomyopathy characterized by chest pain, typically manifesting transient left ventricular (LV) apical akinesis, and ischemic electrocardiographic changes, mimicking acute coronary syndrome (ACS). Although ventricular septal perforation (VSP) is a rare complication of TCM, it is potentially life-threatening if left untreated. Whether the conventional electrocardiographic criteria for TCM are beneficial, even in patients of TCM with VSP, remains unclear.

Case presentation: An 87-year-old woman was admitted for worsening dyspnea. Elevated serum cardiac enzyme levels, LV dysfunction on echocardiography, and ST-segment elevation in leads V1–4 on electrocardiogram were initially suggestive of ACS. An emergency coronary angiography revealed 90 % focal stenosis of the mid-portion of the right coronary artery (RCA) with Thrombolysis in Myocardial Infarction flow grade 2. However, left ventriculography revealed LV apical ballooning with a coexisting left-to-right shunting, which was beyond single RCA distributions, leading to a final diagnosis of TCM with VSP. Repeat echocardiography confirmed VSP and right ventricular involvement with severe pulmonary hypertension. Following successful percutaneous coronary intervention with a drug-eluting stent for RCA stenosis, the patient was managed with medical treatment without surgical intervention. Eventually, VSP and associated pulmonary hypertension markedly improved along with the normalization of the patient's cardiac structure and function. The patient's clinical course was uneventful at the 1-year follow-up.

Conclusions: Herein, we describe the case of TCM with VSP that we successfully managed with medical treatments. Our case highlights the significance of elucidating this rare complication of TCM, pitfalls of the conventional electrocardiographic diagnostic criteria for TCM, and potential of this unique electrocardiographic pattern for identifying TCM-associated VSP.

1. Introduction

Takotsubo cardiomyopathy (TCM), also known as stress cardiomyopathy, apical ballooning syndrome, or broken heart syndrome,

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is a nonischemic disorder characterized by transient regional wall motion abnormalities (WMAs) of the left ventricle [1]. Although TCM shares similar clinical manifestations to acute coronary syndrome (ACS), it requires distinct treatment. Therefore, several valuable electrocardiographic criteria have been proposed to help differentiate TCM from ACS [2,3]. Although most patients with TCM generally show favorable clinical course, some develop acute complications [4,5]. Particularly, ventricular septal perforation (VSP) is a rare mechanical complication of TCM that is potentially fatal if left untreated. However, early diagnosis and appropriate management of VSP remain unclear. Herein, we describe a patient of TCM with VSP who presented with a unique electrocardiographic pattern of ST-segment elevation (STe) in the right precordial leads V1–4. We also conducted a systematic review of case reports of TCM with VSP and searched for the validity of the conventional electrocardiographic criteria for TCM in such patients.

2. CASE presentation

An 87-year-old woman was referred to our hospital for dyspnea. 3 days before visiting our hospital, the patient visited her primary physician for high-grade fever, dyspnea, and hematuria and was treated with an oral antimicrobial agent (levofloxacin, 500 mg/day). However, the patient's condition did not improve, with which the respiratory distress worsened. The patient had a medical history of hypertension, diabetes, dementia, and deep vein thrombosis. The pre-admission medications included candesartan (8 mg/day), teneligliptin (20 mg/day), donepezil (5 mg/day), digoxin (0.125 mg/day), and apixaban (2.5 mg twice daily). Initial assessment of vital signs showed: blood pressure, 92/66 mmHg; heart rate, 92 beats/min; body temperature, 36.7 °C; respiratory rate, 24 breaths/min; and oxygen saturation, 97 % on ambient air. Arterial blood gas analysis revealed pH, 7.454; partial pressure of oxygen, 73.7 mmHg; partial pressure of carbon dioxide, 28.8 mmHg; and bicarbonate level, 19.7 mmol/L. Physical examination revealed a grade 4/6 pansystolic cardiac murmur at the apex and mild abdominal tenderness in the right upper quadrant. An electrocardiogram (ECG)

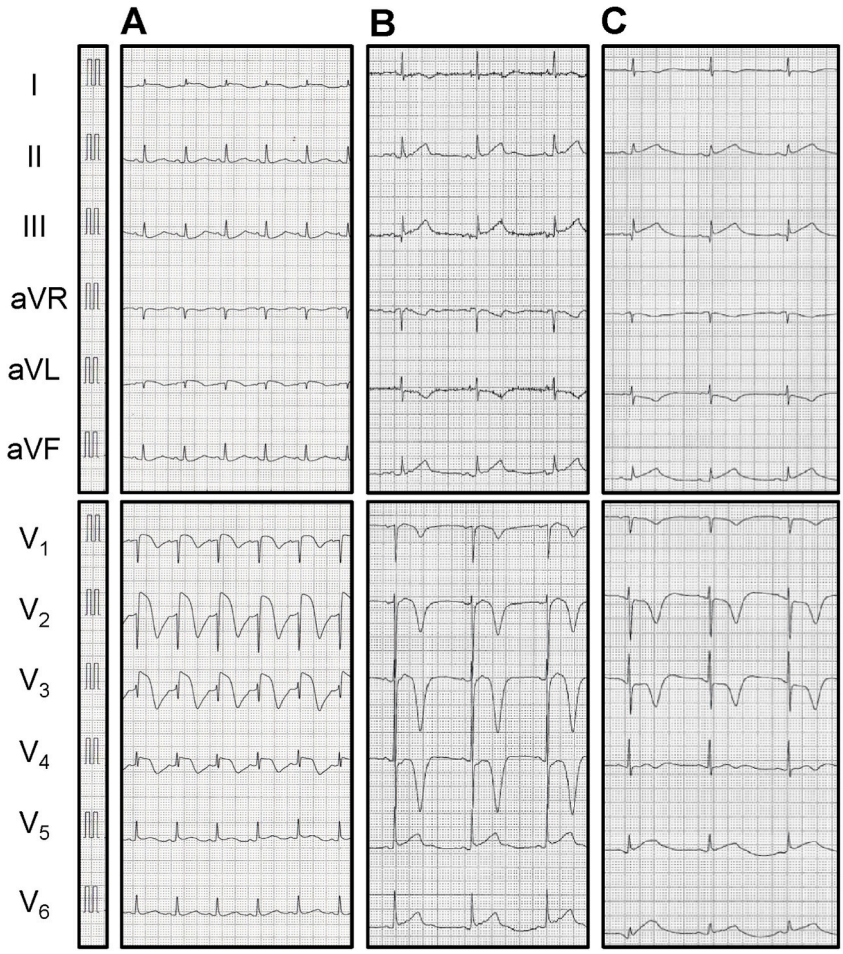

Fig. 1. Time-course of the dynamic electrocardiographic changes
Electrocardiogram (ECG) on admission (A), on day 37 (B), and on day 47 (C) after admission. Prominent ST-segment elevation in leads V1–4, I, and aVL. The lack of an ST-segment depression in lead aVR is noted (A). Profound T-wave inversion in leads V1–4, I, aVL, and corrected QT (QTc) interval prolongation (528 ms) are shown in (B). T-wave inversion in leads V1-3 and QTc interval prolongation (493 ms) persist (C). The ECG paper is set to a standard speed of 25 mm/s and a voltage (amplitude) of 10 mm/mV.

revealed sinus tachycardia and STe in leads V1–4, I, and aVL (Fig. 1A). Chest radiography indicated unremarkable findings. Laboratory test results showed white blood cell count, 18,300/μL (reference: 3,300–8,600/μL) with 78.0 % of neutrophils; C-reactive protein level, 18.05 mg/dL (normal: <0.03 mg/dL); elevated levels of brain natriuretic peptide, 224 pg/mL (normal: <18.4 pg/mL); and troponin T, 0.54 ng/mL (normal: <0.01 ng/mL). Liver and kidney function tests and urinalysis indicated findings within normal range. Initial echocardiography showed akinesis of the apical mid-segments of the left ventricle. The constellation of STe on ECG, left ventricular (LV) WMAs, and elevated serum cardiac enzyme levels was highly suggestive of STe-ACS. Emergency coronary angiography detected unremarkable findings except for 90 % focal stenosis of the mid-portion of the right coronary artery (RCA) with Thrombolysis in Myocardial Infarction flow grade 2 (Fig. 2A and B; and Video S1). However, left ventriculography revealed LV apical ballooning with left-to-right shunting, suggesting VSP (Fig. 2C–F; and Videos S2, S3). LV WMAs extended beyond single RCA distributions, leading to a

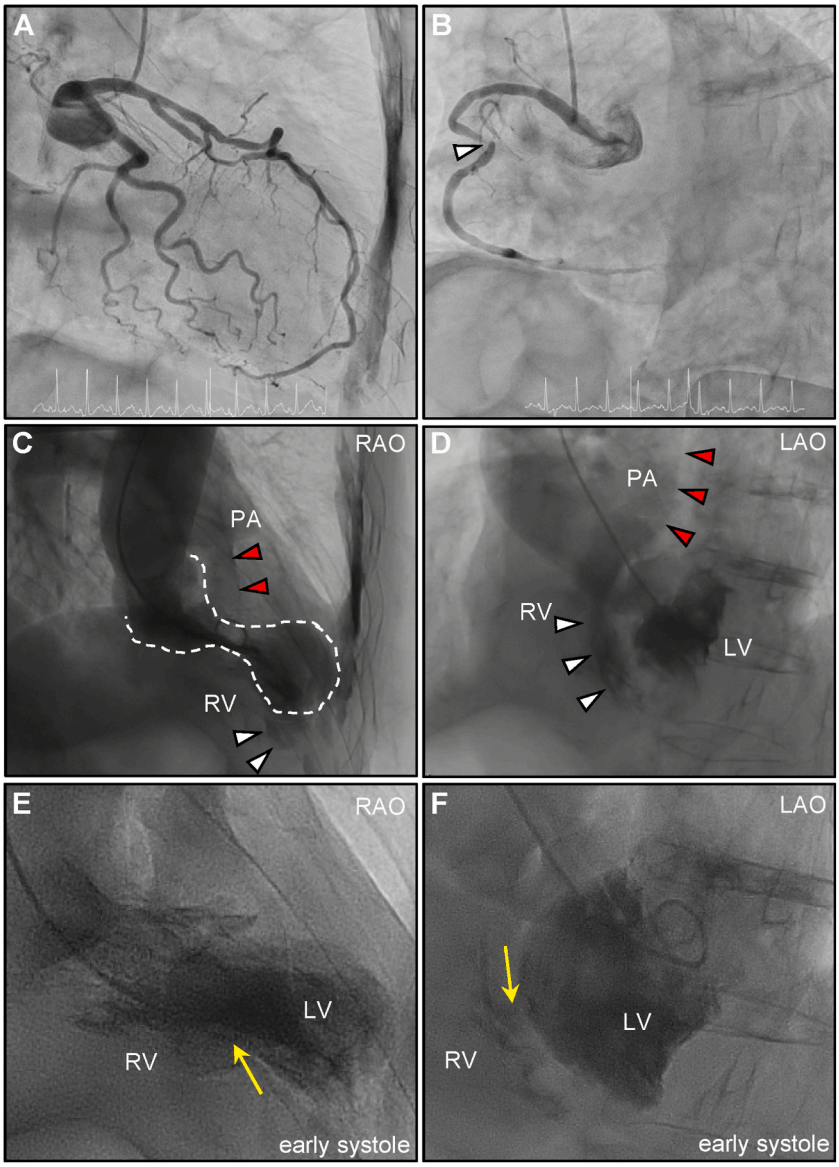

Fig. 2. Cardiac catheterization
Coronary angiography (A, RAO cranial view; B, LAO caudal view). There is no significant stenosis of the left coronary artery. However, 90 % focal stenosis of the mid-right coronary artery is observed (arrowhead). The intact RV branch is shown. Left ventriculography showing apical ballooning of the LV during systole (white dotted line) (C, RAO view; D, LAO view). Notably, the contrast medium simultaneously fills both the RV (white arrowheads) and PA (red arrowheads) through the fistula from the left to right ventricle. Magnified images of early diastolic left ventriculography showing the shunt-flow (arrows) communicating from the left to right ventricle at the boundary region between LV basal wall hypercontraction and LV apical ballooning (E, RAO view; F, LAO view). LAO, left anterior oblique, LV, left ventricle; PA, pulmonary artery; RAO, right anterior oblique; RV, right ventricle.

final diagnosis of TCM with VSP. Considering the risk of hemodynamic compromise in case of progression of the RCA stenotic lesion in addition to the LV WMAs, a subsequent percutaneous coronary intervention (PCI) with a drug-eluting stent was successfully performed, followed by low-dose aspirin (100 mg/day) and prasugrel (3.75 mg/day) administration after a loading dose. After being transferred to the intensive care unit, the patient developed acute heart failure and required oxygen therapy. Her vital signs were as follows: blood pressure, 128/73 mmHg; heart rate, 71 beats/min; respiratory rate, 28 breaths/min; and oxygen saturation, 90 % (at 5L/min of oxygen delivered via a facial mask). Computed tomography (CT) revealed lung congestion and acute cholecystitis with thickening of the gallbladder wall and gallstone wedged in the neck (Fig. 3). Ceftazidime (2 g) was administered intravenously every 12 h for presumptive biliary infection after the collection of two sets of blood cultures. Repeat echocardiography confirmed VSP with a calculated pulmonary-to-systemic blood flow ratio (Qp/Qs) of 2.4 and an enlarged right ventricle with akinesis of the apical segment of the right ventricular (RV) free wall in addition to LV WMAs. Notably, severe pulmonary hypertension (PH), corresponding to an estimated pulmonary artery systolic pressure of 71.7 mmHg was observed (Fig. 4A and Video S4). A thorough discussion with the heart team concluded that emergency surgical repair of the VSP was a very high surgical risk due to the patient's advanced age, comorbidities, and uncontrolled infection. Since the patient's hemodynamic status was stable, we opted for medical therapy with intravenous furosemide administration (20 mg twice daily) to ameliorate the lung congestion, followed by oral diuretics with a vasopressin V2-receptor antagonist (tolvaptan, 15 mg/day), a loop diuretic (azosemide, 30 mg/day), and a mineralocorticoid receptor antagonist (spironolactone, 25 mg/day). Simultaneously, oral diazepam (2mg, taken 3 times a day) was administered for anxiety. In addition, a beta-blocker (bisoprolol, 1.25 mg/day) was added. Subsequently, the patient's condition gradually improved. On day 7 after admission, all blood cultures collected on admission yielded no growth. After confirming improvements in both serological inflammatory markers and abnormal findings on the follow-up CT, antimicrobial therapy was discontinued. Follow-up handheld echocardiography showed significant improvement in WMAs of both ventricles 10 days after admission, with improvement in the concomitant left-to-right shunt flow and PH. An early aspirin discontinuation was performed 2 weeks after PCI. The patient's condition did not progress to cardiogenic shock (CS) during medical therapy. On day 47, all the above findings were almost fully recovered, except for residual VSP, which was confirmed by serial echocardiography and enhanced cardiac CT (Fig. 4B–D and Video S5). Simultaneously, dynamic electrocardiographic changes were observed (Fig. 1B and C). The patient's clinical course was good. However, due to an outbreak of severe acute respiratory syndrome coronavirus 2, discharge was delayed till day 88. Medications at hospital discharge included candesartan (8 mg/day), teneligliptin (20 mg/day), donepezil (5 mg/day), apixaban (2.5 mg twice daily), prasugrel (3.75 mg/day), pitavastatin (1 mg/day), tolvaptan (15 mg/day), azosemide (30 mg/day), spironolactone (25 mg/day), and bisoprolol (1.25 mg/day). Thereafter, the patient had been admitted to a nursing home for long-term care owing to dementia progression. The patient remained healthy without heart failure recurrence at a 1-year phone interview follow-up, and prasugrel was discontinued. A timeline diagram illustrating this case presentation is shown in Fig. 5.

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3. Discussion

3.1. Overview of TCM and systematic review of TCM-associated VSP

Widely accepted diagnostic criteria and general management of TCM are summarized in Table 1 [3,6,7]. TCM, often triggered by emotional or physical stress, generally manifests the classical form characterized by LV apical ballooning. However, there are less common variant forms of TCM, in which LV apex is not affected, including mid-ventricular, basal, and focal variants. Furthermore, focusing on RV involvement, approximately one-third of cases may involve biventricle. Sporadic isolated RV involvement has also been reported [4,8,9]. TCM occurs in approximately 2 percent of patients with suspected ACS [1]. Approximately 90 % of patients with TCM occurred in postmenopausal women in their 60s [4]. Although the proposed mechanisms include catecholamine excess, coronary

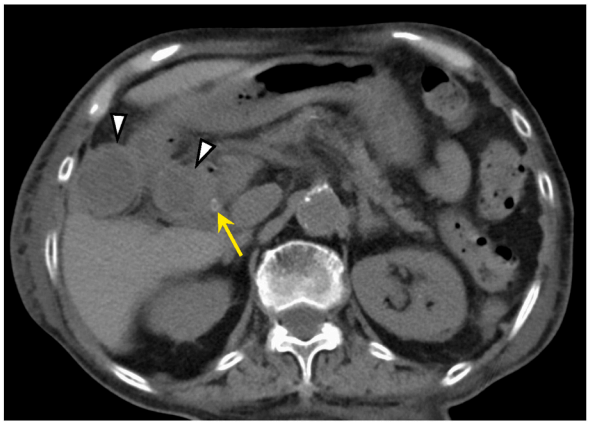


Fig. 3. Abdominal computed tomography (CT) Unenhanced CT showing a distended gallbladder with a wall thickening (arrowheads) and fat strands surrounding tissue. Calcified stone wedging the neck of the gallbladder (arrow).

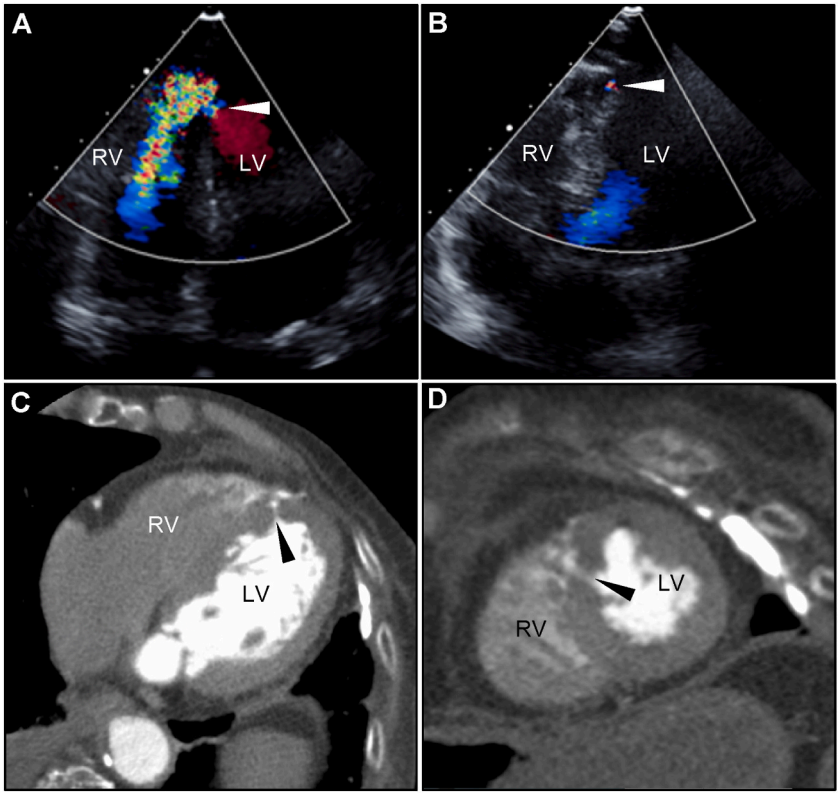


Fig. 4. Serial transthoracic echocardiography (TTE) and cardiac computed tomography angiography (CCTA)
Color Doppler TTEs in the apical 4-chamber view on admission (A) and 47 days after admission (B). Initial TTE shows systolic apical ballooning of the LV concurrent with hyperkinesis of the basal walls, accompanied by a massive left-to-right shunt flow (arrowhead) and marked pulmonary hypertension (calculated Qp/Qs, 2.4; VSP, 3.7 mm; and estimated PASP, 71.7 mmHg) with an enlarged RV (A). Follow-up TTE showing significant improvements in LV function (LV ejection fraction of 60 %), left-to-right shunt flow (arrowhead), and pulmonary hypertension (calculated Qp/Qs, 1.2; VSP, 0.8 mm; and estimated PASP, 24 mmHg) (B). The 4-chamber view (C) and short-axis view (D) of diastolic CCTA performed 47 days after admission. CCTA reveals the residual VSP in the apico-anteroseptal wall of the LV (arrowheads) with an enlarged RV. LV, left ventricle; PASP, pulmonary artery systolic pressure; Qp/Qs, pulmonary-to-systemic blood flow ratio; RV, right ventricle; VSP, ventricular septal perforation.

microvascular dysfunction (CMD), and multivessel epicardial spasms, the exact mechanisms underlying TCM remain poorly understood [1]. TCM is generally recognized as a favorable disease because transient systolic ventricular dysfunction fully recovers within 1–4 weeks. However, the subgroup of patients who develop acute complications, such as acute heart failure, CS, life-threatening arrhythmias, LV outflow tract obstruction, and thromboembolism, has poor in-hospital outcomes compared with those in patients with ACS [4,5]. In addition, the mechanical complications of TCM, including cardiac rupture (CR) and VSP, are rare but potentially life-threatening. The International Takotsubo Registry study that included 1750 patients with TCM showed that the incidence of CR was 0.2 % [4]. A small study comparing patients with TCM with and without CR revealed that potential risk factors for CR included female sex, older age, persistent STe on ECG, and higher LV ejection fraction/systolic blood pressure/diastolic blood pressure/double product/systolic LV pressure [10]. In another study, multivariate logistic regression analysis indicated that a high global registry of acute coronary events (GRACE) risk score [11] and the presence of STe in lead III are significantly associated with CR occurrence in patients with TCM [12]. Given the patient's advanced age, female sex, and high GRACE risk score of 199 points (Table 2), the present case corresponded to a high-risk group for CR.

Although data on the mechanical complications in patients with TCM are available, the number of case reports on TCM with VSP is small. Therefore, we conducted an updated systematic review of case reports of TCM with VSP to evaluate electrocardiographic characteristics and management (Table 3). A literature search was conducted using the electronic databases of PubMed and Ichushi-Web (the database of the Japan Medical Abstracts Society) for articles published between January 1st, 2005 and September 23rd, 2024. We used the following terms in English, or those with similar meanings in Japanese: (i) "Takotsubo cardiomyopathy" or "Stress cardiomyopathy" or "Apical ballooning syndrome" or "Broken heart syndrome", and (ii) "Ventricular septal perforation" or "Ventricular septal rupture". Finally, 28 cases were identified [12–38]: 23 articles were published in English and 4 in Japanese. The majority of cases of TCM with VSP were older patients in their 70s and above, with female sex preponderance (89 %). The time from TCM onset to VSP was frequently within 24 hours (50 %), with most VSP occurring within 3 days, but may last up to 3 months. The VSP was commonly single variously ranging between 5 and 30 mm in size. For case reports providing information on VSP size, there was no consistency between VSP size and in-hospital outcomes. More than half of the patients presented with CS on admission or during

3 days prior to admission

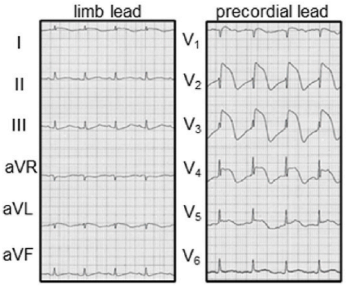
- An 87-year-old woman visited her primary physician for high-grade fever, dyspnea, and hematuria, who was treated with an oral antimicrobial agent (levofloxacin, 500 mg/day)

On admission

- The patient was admitted to our hospital for dyspnea
- Vital signs: BP 92/66 mmHg; HR 92 beats/min; BT 36.7 °C; RR, 24 breaths/min; and SpO_2, 97%
- PE: pansystolic cardiac murmur and abdominal tenderness in the RUQ

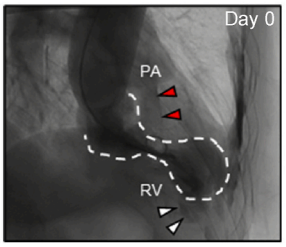
Presumptive diagnosis

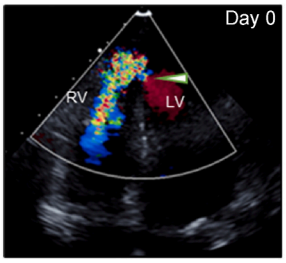
- Elevated serum cardiac enzyme levels, LV dysfunction on echo, and STe in leads V1–4 on ECG were initially suggestive of ACS



Final diagnosis

- CAG showed 90% stenosis of the RCA with TIMI flow grade 2
- LVG showed LV apical ballooning with a left-to-right shunting, which was beyond single RCA distributions
- Color doppler echo confirmed VSP with severe PH (Qp/Qs, 2.4; VSP, 3.7 mm; and PASP, 71.7 mmHg)
- Abdominal CT indicated acute calculous cholecystitis and pulmonary congestion suggestive of congestive heart failure
- A final diagnosis of TCM with VSP with concurrent CAD was made



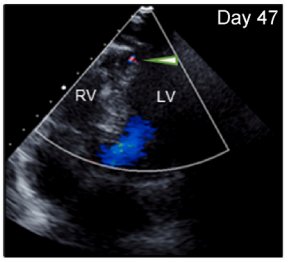


Conventional treatment

- Conventionally, the hemodynamically unstable patients with TCM with VSP undergo surgical repair by attaching patch or percutaneous VSP closure with an occluder device under X-ray guidance

Key treatment of our case

- A drug-eluting stent was emergently deployed for the RCA stenosis
- Ceftazidime was administered for presumptive biliary infection (IV 2g x 2)
- Supportive treatment was opted for achieving hemodynamic stability in our patient (i) to avoid mechanical wall stress without inadvertent use of inotropes, (ii) to inhibit sympathetic activation with sedatives and beta-blockers, and (iii) to control volume overload with combinations of diuretics

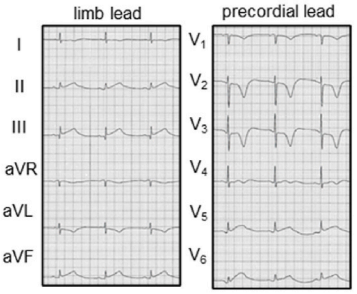


On day 10

- The patient's clinical course was good without cardiogenic shock
- Echo showed significant improvement in LV WMAs, VSP flow, and PH

On day 47

- All the above findings were almost fully recovered except for residual VSP on echo (Qp/Qs, 1.2; VSP, 0.8 mm; and PASP, 24 mmHg)
- ECG revealed Tinv in V1-3 and prolonged QTc interval (493 ms)



On day 88

- After hospital discharge, the patient has been admitted to a nursing-home for long-term care owing to progressive dementia

1-year follow-up

- The patient remained healthy without recurrence of heart failure as assessed at follow-up using telephone interview

(caption on next page)

Fig. 5. A timeline diagram illustrating this case presentation Abbreviations: ACS, acute coronary syndrome; BP, blood pressure; BT, blood temperature; CAD, coronary artery disease; CAG, coronary angiography; CT, computed tomography; ECG, electrocardiogram; HR, heart rate; PE, physical examination; LVG, left ventriculography; LV, left ventricular; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; Qp/Qs, pulmonary-to-systemic blood flow ratio; QTc, corrected QT; RCA, right coronary artery; RR, respiratory rate; RUQ, right upper quadrant; RV, right ventricle; SpO_2, pulse oximetry; STe, ST-segment elevation; TCM, takotsubo cardiomyopathy; TIMI, Thrombolysis in Myocardial Infarction; Tinv, T-wave inversion; VSP, ventricular septal perforation; WMAs, wall motion abnormalities.

Table 1
Diagnosis and management of patients with Takotsubo cardiomyopathy (TCM).

Mayo clinic diagnostic criteria for TCM[6]					
All of the following are required for establishing TCM diagnosis 1) Transient LV systolic dysfunction. The WMAs are typically regional and extend beyond a single epicardial coronary distribution; rare exceptions include the focal and global type. 2) Absence of obstructive CAD or angiographic evidence of acute plaque rupture. If CAD is found, TCM diagnosis can still be made if the WMAs are not in the distribution of CAD. 3) New ECG abnormalities (STe and/or Tinv) or modest elevation in serum cardiac troponin. 4) Absence of pheochromocytoma or myocarditis.					
ECG criteria for differentiating STe-TCM from STe-ACS [3] TCM versus ACS in the setting of STe					
Specific criteria for TCM	Sensitivity	Specificity	PPV	NPV	*p* value
STe in –aVR	43 %	95 %	91 %	62 %	<0.001
STe in –aVR and lack of STe in V1	38 %	95 %	89 %	59 %	<0.001
General management for TCM based on expert consensus[7]					
Clinical scenarios and respective treatments **A) Hemodynamically stable TCM** **Supportive therapy** Managing patients at a cardiology unit with telemetry monitoring. Physical or emotional stress should be removed. LV dysfunction should be treated with guideline-directed medical therapy for heart failure. Anticoagulation is recommended in patients with LV thrombus or severe LV dysfunction. **Acute heart failure** Managing patients at an intensive care unit with close monitoring. Oxygen and assisted ventilation as needed. Diuretics are needed for removing volume overload. Vasodilators are needed for ameliorating LV afterload. Inotropes should be avoided if possible. **B) Hemodynamically unstable TCM** **1) Cardiogenic shock (primary pump failure)** Inotropes should be initiated. MCS (IABP, Impella, or LVAD) should be considered in refractory cases. **2) Cardiogenic shock (LV outflow tract obstruction)** Vasodilators or inotropes should be avoided. Vasopressors such as phenylephrine combined with beta blackade agents are needed.					

Note the limited accuracy of the above ECG criteria in cases of TCM with VSP. STe in right precordial leads may be a red flag for TCM with VSP. Abbreviation. ACS, acute coronary syndrome; CAD, coronary artery disease; ECG, electrocardiographic; IABP, intra-aortic balloon pump; LV, left ventricular; LVAD, left ventricular assist device; MCS, mechanical circulatory support; NPV, negative predictive value; PPV, positive predictive value; STe, ST-segment elevation; Tinv, T-wave inversion; VSP, ventricular septal perforation; WMAs, wall motion abnormalities.

Table 2
GRACE risk score[11] in the current case.

Predictive Factors	Results	Points
Killip Class	I	0
Systolic Blood Pressure (mmHg)	92	53
Heart Rate (beats/min)	75	9
Age (y)	87	91
Creatinine Level (mg/dL)	0.51	4
Cardiac Arrest at Admission	No	0
ST-Segment Deviation	Yes	28
Elevated Cardiac Enzyme Levels	Yes	14
Sum Points for All Predictive Factors		**199**
Probability of In-Hospital Death (%)		**13**

GRACE, global registry of acute coronary events.

Table 3
Electrocardiographic characteristics, treatments, and in-hospital outcomes in patients with Takotsubo cardiomyopathy (TCM) complicated by VSP.

Case	Author	Age	Sex	Initial 12-lead electrocardiographic findings			TCM to	VSP		PASP	CS	MCS	Treatment	VSP to	In-hospital
				STe in V1	STe in –aVR		**VSP time**	Size (mm)	Qp/Qs	(mmHg)				**PC/SR time**	**outcome**
1	Sakai et al.[13]	84	F	(−)	(−)	STe inII, III, aVF, V3–5, Tinv in V2–5	<24 h	NA	1.97	NA	(+)	(+)	Medical		Death
2	Izumi et al.[14]	73	F	(−)	(−)	STe in V2–5	<24 h	25 × 12	2.96	42	(−)	(−)	SR	22 days	Survival
3	Mariscalco et al.[15]	71	F	NA	NA	Anterior leads STe	3 days	NA	NA	NA	(+)	(+)	SR	<24 h	Survival
4	Nishida et al.[16]	70	F	(+)	(−)	STe in V1–3, Tinv in V2–5	<24 h	NA	NA	WNR	(+)	(+)	SR	<24 h	Transfer
5	Minami et al.[17]	70	F	(+)	(−)	STe inII, III, aVF, V1–2, Tinv in V2–6	<24 h	10	2.61	NA	(+)	(+)	SR	NA	NA
6	Aikawa et al.[18]	81	F	(−)	(+)	STe inII, III, aVF, Tinv in V1–5, STd in aVR	<24 h	NA	2.82	NA	(+)	(−)	Medical		Death
7	Ikeda et al.[19]	70s	F	(−)	(−)	Tinv inI,II, aVL, V1–6	<24 h	9	1.8	NA	(−)	NA	SR	10 days	Death
8	Rhyou et al.[20]	87	F	(+)	(−)	STe in V1–5	<24 h	8	NA	NA	(+)	(−)	Medical		Death
9	Ono et al.[21]	66	F	(+)	NA	STe in V1–4	<24 h	10	2.72	NA	(+)	(+)	SR	3 days	Death
10	Pepe et al.[22]	84	F	NA	NA	Anterior leads STe	<24 h	14 × 10	NA	60	(+)	(+)	PC	3 days	Survival
11	Lu et al.[23]	71	F	(−)	NA	STe in V3–6	<24 h	10 × 10	2.2	57	(−)	(−)	PC	11 days	Survival
12	Miyake et al.[24]	73	M	(−)	NA	Q-wave in III, aVF, Tinv in V2–5	2 days	18 × 15	1.9	45	(−)	(−)	SR	13 days	Survival
13	Rodríguez et al.[25]	79	F	(−)	(−)	Tinv in V2–6	3 days	7 × 8	NA	NA	(+)	(−)	PC	7 days	Survival
14	Sung et al.[26]	73	F	(+)	(+)	STe in V1–6, STd in aVR	<24 h	NA	NA	59	(+)	(−)	SR	<24 h	Death
15	Chung et al.[27]	83	F	(+)	(−)	STe in II, III, aVF, V1–5	2 days	6	NA	49	(−)	(−)	SR	2 days	Survival
16	Tsuji et al.[28]	71	F	(−)	(+)	STe inI, aVL, V2–5, STd in aVR	9 days	NA	2.95	NA	(−)	(+)	SR	7 days	Survival
17	Webster et al.[29]	68	F	NA	NA	Anterolateral leads STe	4 days	NA	NA	NA	(+)	(+)	Medical		Death
18	Manna et al.[30]	57	F	(−)	(−)	Q-wave and Tinv in V1–3	3 days	NA	2.7	NA	(+)	(−)	PC/SR	<24 h	Survival
19	Narita et al.[31]	92	M	(+)	(−)	STe and Tinv in V1–4	<24 h	NA	1.46	NA	(−)	(−)	Medical		Survival
20	Sternberg et al.[32]	63	F	(−)	(−)	STe and Tinv in II, III, aVF, V3–6	3 days	NA	NA	NA	(+)	(+)	SR	<24 h	Death
21	Sternberg et al.[32]	80	F	(−)	(−)	STe in V2-4, Q-wave in V1–3	2 weeks	14	2.07	NA	(−)	(−)	SR	<24 h	Survival
22	Zalewska-Adamiec et al.[12]	84	F	(+)	NA	STe inI,aVL,V1–6	2 days	NA	NA	NA	(+)	(−)	Medical		Death
23	Akiyama et al.[33]	80	F	(+)	(−)	STe and Tinv in V1–5	<24 h	NA	2.2	48	(−)	(−)	Medical		Survival
24	Alsheikh et al.[34]	31	M	(+)	NA	STe in V1–6	<24 h	26 × 19	NA	WNR	(−)	(−)	SR	3 days	Survival
25	Yang et al.[35]	77	F	(+)	(−)	STe and Tinv in V1–4	3 months	10.8 × 4.1	NA	69	(+)	(−)	Medical		Survival
26	Yamazaki et al.[36]	76	F	(+)	NA	STe in V1–6	4 days	5 × 5	NA	NA	(−)	(+)	SR	<24 h	Survival
27	Hara et al.[37]	82	F	(+)	NA	STe in V1–6	2 days	10 × 10	NA	NA	(−)	(+)	SR	12 days	Death†
28	Paiva et al.[38]	76	F	(+)	(+)	STe in V1–6, Q-wave in V2–4	11 days	30 × 10	2.3	60–65	(+)	(+)	SR	15 days	Survival
29	Present case	87	F	(+)	(−)	STe in V1–4	<24 h	3.7	2.4	72	(−)	(−)	Medical		Survival

CS, cardiogenic shock; F, female; M, male; MCS, mechanical circulatory support; NA, not available; PC, percutaneous closure; PASP, pulmonary artery systolic pressure; STd, ST-segment depression; STe, ST-segment elevation; SR, surgical repair; Tinv, T-wave inversion; VSP, ventricular septal perforation; WNR, within normal range. *MCS includes intra-aortic balloon pump, impella, or both. †The patient died from pneumonia.

hospitalization (57 %), who often required mechanical circulatory support. The present review revealed a high in-hospital mortality rate of 37 %, with much higher mortality in patients with CS than in those without CS (50 % versus 17 %). Given the short interval between TCM onset and VSP development and the high in-hospital mortality rate, early disease detection and proper management are required. Herein, we describe the case of TCM with VSP presenting with STe in V1–4 that we successfully managed with medical therapy. This case report might provide several valuable clinical insights.

3.2. Trigger of TCM

Our case underscores the significance of acute biliary infection as a possible physical trigger of TCM. In our case, the non-specific symptoms such as fever and dyspnea and absence of intense emotional stress and chest pain were unlikely to raise suspicion of this disorder. Furthermore, STe in the right precordial leads on ECG, and the presence of obstructive coronary artery disease (CAD) led to a delayed TCM diagnosis. Considering that the preadmission antimicrobial therapy might have influenced blood culture results and abdominal CT findings suggested severe cholecystitis, acute biliary sepsis presumably might have been the trigger of TCM in our case. A case report of TCM precipitated by acute cholecystitis has been documented [39]. In addition, a large-scale retrospective cohort study evaluating patients with severe sepsis demonstrated that TCM may occur with an increasing incidence of severe sepsis (from 0.02 % in 2007 to 0.25 % in 2013; $p < 0.001$) with increasing awareness [40], supporting this notion.

3.3. Diagnostic considerations

Our case of TCM with VSP exhibited unique electrocardiographic findings.

STe is frequent in TCM and occurs most commonly in precordial leads, similar to STe-ACS. STe-TCM represents characteristic electrocardiographic findings, including ST-segment depression in aVR (or STe in −aVR) corresponding to LV apical akinesis, lack of STe in V1 corresponding to LV basal wall hypercontraction, and lack of abnormal Q-waves and/or reciprocal changes. Several useful conventional electrocardiographic criteria for differentiating TCM from ACS have been reported in the literature [3]. In patients with acute chest pain with STe, a combination of STe in −aVR and lack of STe in V1, which is considered a hallmark of TCM, was useful for differentiating STe-TCM from STe-ACS (sensitivity, 91 %; specificity, 96 %; $p < 0.001$) [2]. Another study also verified the acceptable diagnostic accuracy of such electrocardiographic criteria [3]: a sole electrocardiographic finding of STe in −aVR (sensitivity, 43 %; specificity, 95 %; positive predictive value, 91 %; and negative predictive value, 62 %; $p < 0.001$). It also revealed a combination of STe in −aVR and lack of STe in V1 (sensitivity, 38 %; specificity, 95 %; positive predictive value, 89 %; and negative predictive value, 59 %; $p < 0.001$). Conversely, the present case showed an STe in V1 and lack of STe in −aVR, none of which was true according to the previous electrocardiographic criteria for TCM. Limited to case reports with a detectable 12-lead ECG, our case review revealed the relatively low sensitivity of TCM diagnosis, including the single electrocardiographic finding of STe in −aVR (sensitivity, 22 %; 4 of 18) or the combined electrocardiographic finding of STe in −aVR and lack of STe in V1 (sensitivity, 11 %; 2 of 18), suggesting the limited accuracy of the conventional electrocardiographic criteria in cases of TCM with VSP.

3.4. Clinical implications

The following 3 possible factors may have been involved in the unique electrocardiographic features of STe in V1–4 in our case. Considering that STe on ECG is a hallmark of acute transmural ischemia and right precordial leads V1–3/4 face the anterior RV wall in the case of RV enlargement, RV transmural ischemia might be a crucial mechanism for generating such electrocardiographic findings. First, the right ventricle was vulnerable to the acute increase in afterload caused by VSP and was unable to generate a sufficient RV stroke volume to match, leading to an increased RV oxygen demand. Simultaneously, LV dysfunction could reduce the cardiac output with coronary perfusion, which triggered RV tissue hypoxia. Second, RV involvement in TCM could be attributed to increased RV strain, leading to increased RV oxygen demand. Third, significant RCA stenosis might have contributed to further RV supply ischemia. As a result, severe RV transmural ischemia might be highly likely to cause STe in V1–4 in the present case. Similarly, patients with acute pulmonary thromboembolism present with STe in the right precordial leads V1–3/4, where RV transmural ischemia induced by acute PH has been proposed as the underlying mechanism of such electrocardiographic changes [41]. Therefore, acute PH may be the key to generating such electrocardiographic changes in patients of TCM with VSP. Approximately half of the cases of TCM with VSP exhibited the same STe in the right precordial leads, including V1, as in our case (50 %, 14/28) (Table 3). Similarly, limited to case reports providing information on PH, a high proportion of patients of TCM with VSP had concomitant PH (82 %, 9 of 11 cases), supporting this notion. Based on the above findings, the present case highlights the pitfalls of conventional electrocardiographic criteria in cases of TCM with VSP and the diagnostic potential of STe in V1 as a red flag for TCM-associated VSP. Future comparative electrocardiographic analyses between patients of TCM with and without VSP are required to validate our results. In addition, the proposed electrocardiographic criteria for differentiating STe-TCM from STe-ACS as well as new electrocardiographic findings obtained from this case are presented in Table 1.

3.5. Proposed pathomechanism

Although the exact pathomechanism underlying VSP in patients with TCM remains unknown, it might be multifactorial. Pathologies in previous case reports and case series of TCM with CR revealed histological similarities between both TCM and ACS complicated by CR [42]. The histological findings at the site of CR included coagulation myocyte necrosis, mononuclear lymphocyte

infiltrations, bundles of wavy myocardial fibers, and patchy infarction of myocardial fibers. These findings are commonly observed in patients with myocardial infarction, in addition to contraction band necrosis suggestive of catecholamine excess that is commonly observed in those with TCM. Furthermore, there is increasing evidence supporting the potential role of CMD in the pathogenesis of TCM. A prospective comparative study showed that severely impaired coronary microvascular reactivity in response to either intracoronary acetylcholine or adenosine was often observed in most postmenopausal women with TCM compared with those in the control group, suggestive of CMD [43]. Additionally, a myocardial contrast echocardiography study demonstrated transient CMD during the acute phase in patients with TCM [44]. Another case report of TCM showed perfusion abnormalities in the LV lesion on radionuclide myocardial perfusion imaging as well as CMD on coronary perfusion examination during the acute phase. However, all of these resolved completely during the recovery phase, suggesting that CMD may trigger myocardial ischemia in patients with TCM [45]. In the present case, VSP occurred at the hinge point between LV basal wall hypercontraction and LV apical ballooning. Therefore, in the presence of CMD, sympathetic hyperactivity, catecholamine excess, and mechanical wall stress at the hinge point might have induced severe acute ischemia, leading to ongoing vulnerable myocardial damage, susceptible to LV perforation.

3.6. Management strategies

Currently, there are no guidelines for the management of TCM-associated VSP. In addition, the proper timing for the surgical repair of VSP remains unclear. Our review revealed a higher postoperative cardiac-related death in patients who underwent urgent or semi-urgent surgery within 3 days after VSP development than in those who underwent later surgery (33 % versus 17 %). It is presumably due to impaired LV systolic function concurrent with hemodynamic instability during the acute phase. Based on these poor surgical outcomes, a less invasive approach with percutaneous closure of VSP may improve survival due to early hemodynamic stabilization. Limited to 4 patients who underwent percutaneous closure [22,23,25,30], this approach revealed a relatively high success rate of 75 % in treating VSPs. However, these observations may reflect a selection bias, as the procedure was performed in a subgroup of patients during the recovery phase of LV systolic function at a low surgical risk. Here, we opted for supportive therapy owing to the high surgical risk and stable hemodynamic status. Considering the risk of infection spread, we avoided using an intra-aortic balloon pump support. Our patient showed maintained hemodynamic stability without developing CS during hospitalization. Using conservative therapy, the VSP size and concurrent PH considerably improved as LV systolic function recovered. Generally, LV dysfunction and associated LV morphological changes are reversible in patients with TCM, which are distinct from those in patients with ACS. Therefore, in the present case, the restoration of LV geometry with improvement in LV dysfunction may have reduced the VSP size, resulting in reduced left-to-right shunt flow and improved PH. Presumably, avoiding mechanical wall stress exacerbation using inadvertent inotropic support, ameliorating sympathetic activation using sedatives and beta blockade, and controlling volume overload using diuretics might lead to early withdrawal from the acute phase of TCM with favorable outcomes in our case. Moreover, a combined decongestion treatment consisting of loop diuretic, mineralocorticoid receptor antagonist, and vasopressin V2-receptor antagonist might be useful for safely achieving euvolemia without causing hypotension due to intravascular dehydration [46]. Similarly, several case reports have suggested that patients with hemodynamic stability maintained showed good outcomes even after medical therapy [31,33,35]. Therefore, considering the high risk of early surgery in patients with VSP during the acute phase, medical treatment may be an effective treatment option for TCM-associated VSP as long as hemodynamics is preserved. However, the selection of patients that could be treatable with non-invasive medical therapy remains challenging, and further studies are required to confirm this hypothesis.

3.7. Limitations

This case report and systematic review have the following three limitations.

The first is the selection bias of the articles that we searched using only PubMed and the Ichu-shi Web databases in the present study. In addition, the target languages were limited to English and Japanese. Hence, we might have missed some papers reported in other databases or languages.

Second, our patient underwent emergent PCI during the acute phase of TCM with VSP. Considering the therapeutic potential of urgent surgical intervention to VSP, it was a very tough decision to perform emergent PCI in the present case of TCM with VSP receiving an oral anticoagulant (OAC). Current guidelines recommend that in patients with ACS, a dual antiplatelet therapy of aspirin plus P2Y12 inhibitor is recommended for 12 months after implantation of drug-eluting stents unless there are contraindications including excessive risk of bleeding (Class of recommendation I, Level of evidence A) [47]. However, our patients had a high bleeding risk and underwent an emergent PCI followed by triple antithrombotic therapy consisting of aspirin, P2Y12 inhibitor, and OAC [48]. Although a regimen of triple antithrombotic therapy is the standard in patients with atrial fibrillation undergoing PCI, a meta-analysis of randomized controlled trials showed that OAC plus P2PY12 inhibitor favor less bleeding compared with triple antithrombotic therapy [49]. Furthermore, a randomized controlled trial conducted in Japan showed that OAC alone was superior to combination therapy of OAC plus a single antiplatelet for safety despite both groups having similar efficacy in patients with atrial fibrillation and stable CAD 12 months after PCI [50]. Therefore, the triple antithrombotic therapy in our case followed this previously described regimen. Although approximately 15 % of patients with TCM have concomitant CAD [4], no guideline-recommended therapy is available for severe CAD in patients of TCM with VSP. This is an important issue to be resolved in future research.

Finally, detailed information on TCM-associated VSP in our systematic review was limited. In a single-center retrospective cohort study evaluating 127 patients with post-myocardial infarction VSP, the multivariate Cox regression analysis demonstrated that neither VSP size [adjusted hazard ratio (HR), 1.02; 95 % confidence interval (CI), 0.95–1.09; $p = 0.687$] nor location (anterior: adjusted HR,

0.71; 95 % CI, 0.20–2.51; $p = 0.597$; and posterior: adjusted HR, 0.91; 95 % CI, 0.21–3.95; $p = 0.897$) were relevant to long-term mortalities [51]. However, the small sample sizes in our systematic review were not sufficient for statistical analysis of the relationship between VSP and in-hospital mortality in patients of TCM with VSP. Therefore, further accumulation of data on this relationship is warranted.

4. Conclusions

Herein, we describe the case of TCM with VSP presenting with STe in V1–4, successfully managed with medical treatment. Our case indicated that this electrocardiographic feature could be a new red flag for TCM-associated VSP. Since VSP could be a fatal complication of TCM, early diagnosis and proper treatment are essential. Therefore, clinicians should pay close attention to this rare complication of TCM and consider this disease entity as a differential diagnosis in patients presenting with STe in V1–4 in emergency settings.

Consent

Written informed consent for the submission and publication of this case report, including images and associated videos, was obtained from the patient.

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Additional information

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CRediT authorship contribution statement

Shogo Haruki: Data curation. **Hiroyuki Yamamoto:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Jun Isogai:** Writing – original draft, Validation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38812.

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