EJCRIM
European Journal
of Case Reports
in Internal Medicine

ENTRECTINIB-INDUCED BRUGADA SYNDROME LEADING TO VENTRICULAR TACHYCARDIA IN A PATIENT WITH ROS1 FUSION-POSITIVE LUNG ADENOCARCINOMA

Nobuo Ishiguro, Takeshi Mori, Makito Kaneshiro, Shin Hasegawa, Akimitsu Tanaka, Miyuki Ando, Kazuo Kato

Department of Cardiology, Nagoya Tokushukai General Hospital, Nagoya, Japan

Corresponding author's e-mail: i-nobuo@nagoya.tokushukai.or.jp

Received: 06/02/2025
Accepted: 24/02/2025
Published: 02/04/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Signed consent was obtained from the patient.

How to cite this article: Ishiguro N, Mori T, Kaneshiro M, Hasegawa S, Tanaka A, Ando M, Kato K. Entrectinib-induced Brugada syndrome leading to ventricular tachycardia in a patient with ROS1 fusion-positive lung adenocarcinoma. *EJCRIM* 2025;**12**:doi:10.12890/2025_005232

ABSTRACT

A 65-year-old male presented to the emergency room after experiencing syncope while driving, causing a self-inflicted accident. He had previously been diagnosed with stage IV A (cTXN2M1a) lung adenocarcinoma with C-ROS oncogene 1 (ROS1) fusion gene, wherein entrectinib (a multikinase inhibitor of ROS1, 600 mg orally once daily) was initiated as the first-line chemotherapy 12 days prior. He presented with haemodynamically unstable conditions without fever (blood pressure 89/42 mmHg; heart rate, 180/min). The 12-lead electrocardiogram revealed ventricular tachycardia (VT) with a left bundle branch block and right axis deviation. Synchronised electrical cardioversion terminated the sustained VT, and the post-electrocardiogram exhibited coved-type ST-segment elevation in V1 to V3. An emergency coronary angiography showed no abnormal findings. Coved-type ST-segment elevation in V1 to V3 persisted for two days following cessation of entrectinib; however, electrocardiogram findings gradually normalised, with no recurrence of clinical VT. Catheter ablation for VT was initially planned; however, the consultant pulmonologist considered that entrectinib could induce Brugada syndrome (BrS), resulting in sustained VT. Therefore, the plan was suspended and entrectinib was discontinued. Electrophysiological examination with programmed electrical and pilsicainide infusion for risk stratification failed to induce clinical VT, and the patient was considered at low risk for VT recurrence following entrectinib discontinuation. Accordingly, we opted for close observation. At the one-year follow-up, no ventricular arrhythmias were noted. The relationship between entrectinib and drug-induced BrS remains unclear, with few reported cases. Continuous or frequent electrocardiogram monitoring during hospitalisation post entrectinib initiation may help detect entrectinib-induced BrS.

KEYWORDS

Entrectinib, drug-induced Brugada syndrome, ventricular tachycardia, ROS1 fusion-positive non-small-cell lung cancer

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- The relationship between entrectinib and drug-induced Brugada syndrome remains unclear, and reports of entrectinib-induced Brugada syndrome are rare.
- We performed risk stratification using electrophysiological examinations in a case of entrectinib-induced Brugada syndrome in a patient with ROS1 fusion-positive lung adenocarcinoma.
- Our results suggest that continuous electrocardiogram monitoring or frequent electrocardiogram recording at least once a day several days following entrectinib initiation may help detect entrectinib-induced Brugada syndrome irrespective of being in or out of hospital.

INTRODUCTION

Entrectinib is a multikinase inhibitor of C-ROS oncogene 1 (ROS1), tropomyosin receptor kinase A, B, and C, and anaplastic lymphoma kinase. Entrectinib is associated with serious adverse cardiac events including cardiac tamponade, cardiogenic shock, myocarditis and pericardial effusion. These events have been reported in 2% of patients with ROS1 fusion-positive non-small-cell lung cancer[1]. Notably, entrectinib-induced Brugada syndrome (BrS) has been reported in only two cases[2,3]. However, sustained ventricular tachycardia (VT) attributable to entrectinib-induced BrS has not previously been reported.

We present a rare case of entrectinib-induced BrS leading to sustained VT and discuss risk stratification using electrophysiological examinations.

CASE DESCRIPTION

A 65-year-old male with complaints of dyspnoea on exertion and a large left-sided pleural effusion on radiography was referred to the Department of Respiratory Medicine at our hospital. He was an ex-smoker with a medical history of hypertension and hyperuricaemia, with no family history of sudden cardiac death. Pleural fluid cytology findings indicated lung adenocarcinoma with positive thyroid transcription factor-1 expression. Following a thoracoscopic pleural biopsy, the patient was diagnosed with stage IV A (cTXN2M1a) lung adenocarcinoma with ROS1 fusion gene. Entrectinib (600 mg orally once daily) was initiated as the first-line chemotherapy. Twelve days after entrectinib initiation, the patient was brought to the emergency room after experiencing syncope while driving, causing a self-inflicted accident. He complained of fatigue and presented with haemodynamically unstable conditions without fever: body temperature 36.3°C, blood pressure 89/42 mmHg and heart rate 180/min.

The 12-lead electrocardiogram (ECG) showed a wide QRS morphology with left bundle branch block, right axis deviation and an RS interval (time from R wave onset to S wave nadir) of 71 ms *(Fig. 1A)*[4,5], suggesting a VT. Synchronised electrical cardioversion terminated the sustained VT, and an ECG following cardioversion exhibited coved-type ST-segment elevation in V1 to V3 *(Fig. 1B)*. Ultrasound cardiography findings indicated normal left ventricular ejection fraction with no focal asynergy; no significant changes were observed when compared to the findings from 18 days prior. Laboratory data revealed high plasma brain natriuretic peptide and troponin-I levels. Emergency coronary angiography findings indicated no abnormal anatomy nor stenosis in the coronary arteries *(Fig. 2)*. Additionally, an endomyocardial biopsy was performed on samples from the right ventricular septum. The patient was transferred to a high-care unit, and bisoprolol (2.5 mg/day) was prescribed in anticipation of idiopathic VT. Catheter ablation for VT was initially planned. However, the consultant pulmonologist considered that entrectinib could provoke drug-induced BrS, resulting in sustained VT. Therefore, the catheter ablation plan was suspended, and the administration of both entrectinib and bisoprolol was

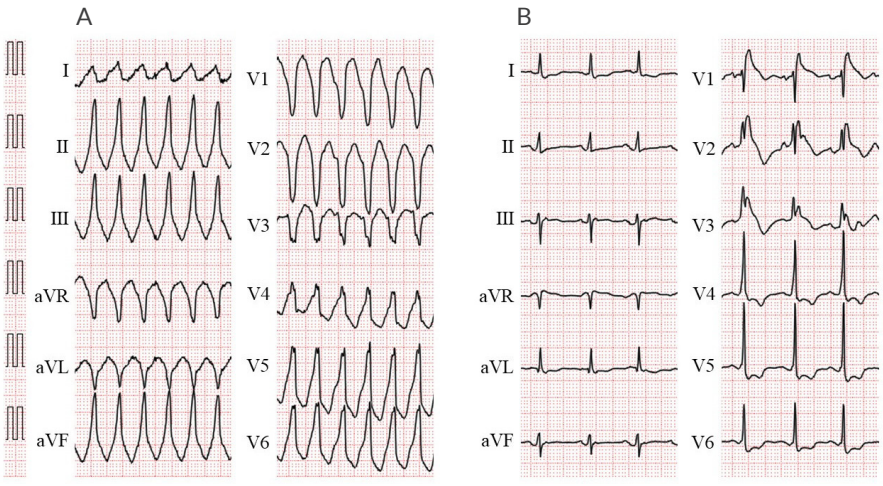

Figure 1. A) The 12-lead electrocardiography (ECG) showed a wide QRS morphology with left bundle branch block, right axis deviation and an RS interval (time from R wave onset to S wave nadir) of 71 ms, suggested as a VT; B) ECG following synchronised electrical cardioversion exhibiting coved-type ST-segment elevation in V1 to V3.

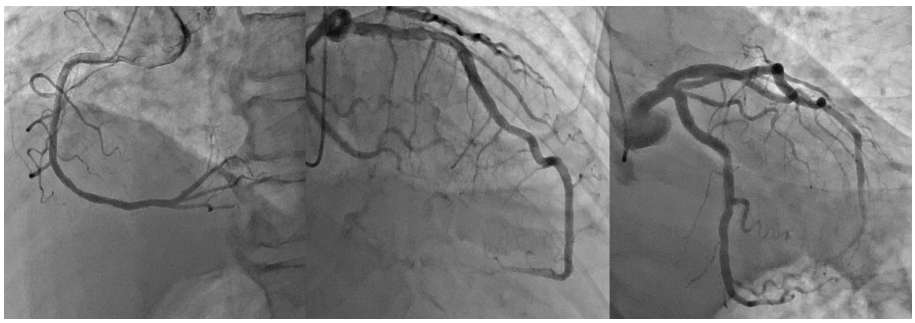

Figure 2. An emergency coronary angiography depicting no abnormal anatomy nor stenosis in the coronary arteries.

discontinued. Coved-type ST-segment elevation in V1 to V3 persisted for two days following cessation of entrectinib. However, the ECG findings gradually normalised and no recurrence of clinical VT was noted *(Fig. 3)*. Late gadolinium enhancement-cardiovascular magnetic resonance imaging on day 2 of hospitalisation demonstrated no delayed enhancement *(Fig. 4A)*. Microscopic investigation of endomyocardial biopsy samples revealed mild interstitial fibrosis on Masson's trichrome staining *(Fig. 4B)*, while haematoxylin and eosin staining indicated no evidence of inflammatory cell infiltration *(Fig. 4C)*. Immunostaining revealed focal CD3-positive T lymphocytes in stroma without obvious cardiomyocyte injury *(Fig. 4D)*.

An electrophysiological examination for risk stratification was performed on day 10 of hospitalisation. Programmed electrical ventricular stimulation was performed by applying burst ventricular pacing up to 240 ms and double extra stimuli from the right ventricular (RV) outflow tract and apex up to their effective refractory periods, but no sustained VT could be induced *(Fig. 5A, B)*. A pilsicainide (sodium channel blocker, available only in Japan) infusion test (1.0 mg/kg) also failed to induce typical coved-type ST-segment elevation *(Fig. 5C)*[6]. Following pilsicainide administration, programmed electrical ventricular stimulation was performed, revealing that the only self-terminated, non-sustained VT was induced by burst pacing from the RV apex at 240 ms intervals *(Fig. 4D)*. Finally, clinical VT could not be induced by any programmed electrical stimulation. Based on these electrophysiological findings, the patient was deemed to be at low risk of VT recurrence after discontinuing entrectinib. Accordingly, we opted for close observation only, and the patient was discharged on day 14 of hospitalisation. At the one-year follow-up, the patient remained free of ventricular arrhythmias.

DISCUSSION

Entrectinib, a multikinase inhibitor of ROS1/tropomyosin receptor kinase, is safe and demonstrates sustained efficacy in patients with ROS1 fusion gene-positive non-small cell lung cancer. Entrectinib was approved in Japan in June 2019. In phase I/II trials, including ALKA-372–001, STARTRK-1 and STARTRK-2, entrectinib-related adverse cardiac events were reported in 2% of patients[1]. While myocarditis is a well-known treatment-related adverse event, drug-induced BrS was not reported in these trials. In this case, myocarditis was excluded as a microscopic investigation of endomyocardial biopsy samples revealed no evidence of inflammatory cell infiltration. Drug-induced BrS is defined as the presence of the Brugada pattern in an ECG and the risk of ventricular arrhythmias after exposure to certain drugs, despite normal

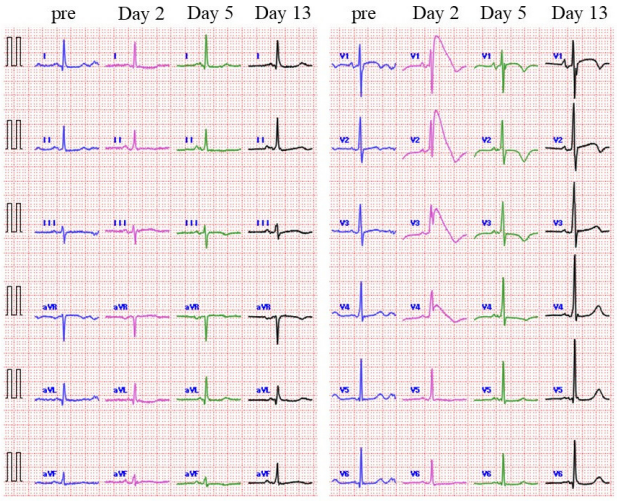

Figure 3. Coved-type ST-segment elevation in V1 to V3 persisted for two days following cessation of entrectinib. The electrocardiography findings then gradually normalised.

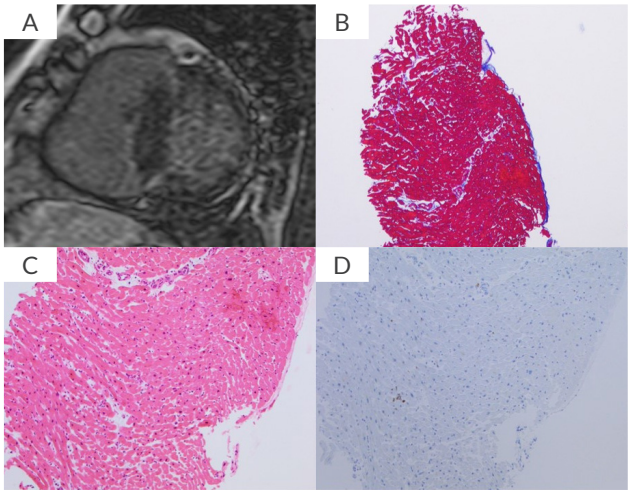

Figure 4. A) Late gadolinium enhancement-cardiovascular magnetic resonance imaging on day 2 of hospitalisation demonstrating no delayed enhancement; B) Microscopic investigation of endomyocardial biopsy samples revealing mild interstitial fibrosis on Masson's trichrome staining; C) Haematoxylin and eosin staining showing no evidence of inflammatory cell infiltration; D) Immunostaining showing focal CD3-positive T lymphocytes in the stroma without evident cardiomyocyte injury.

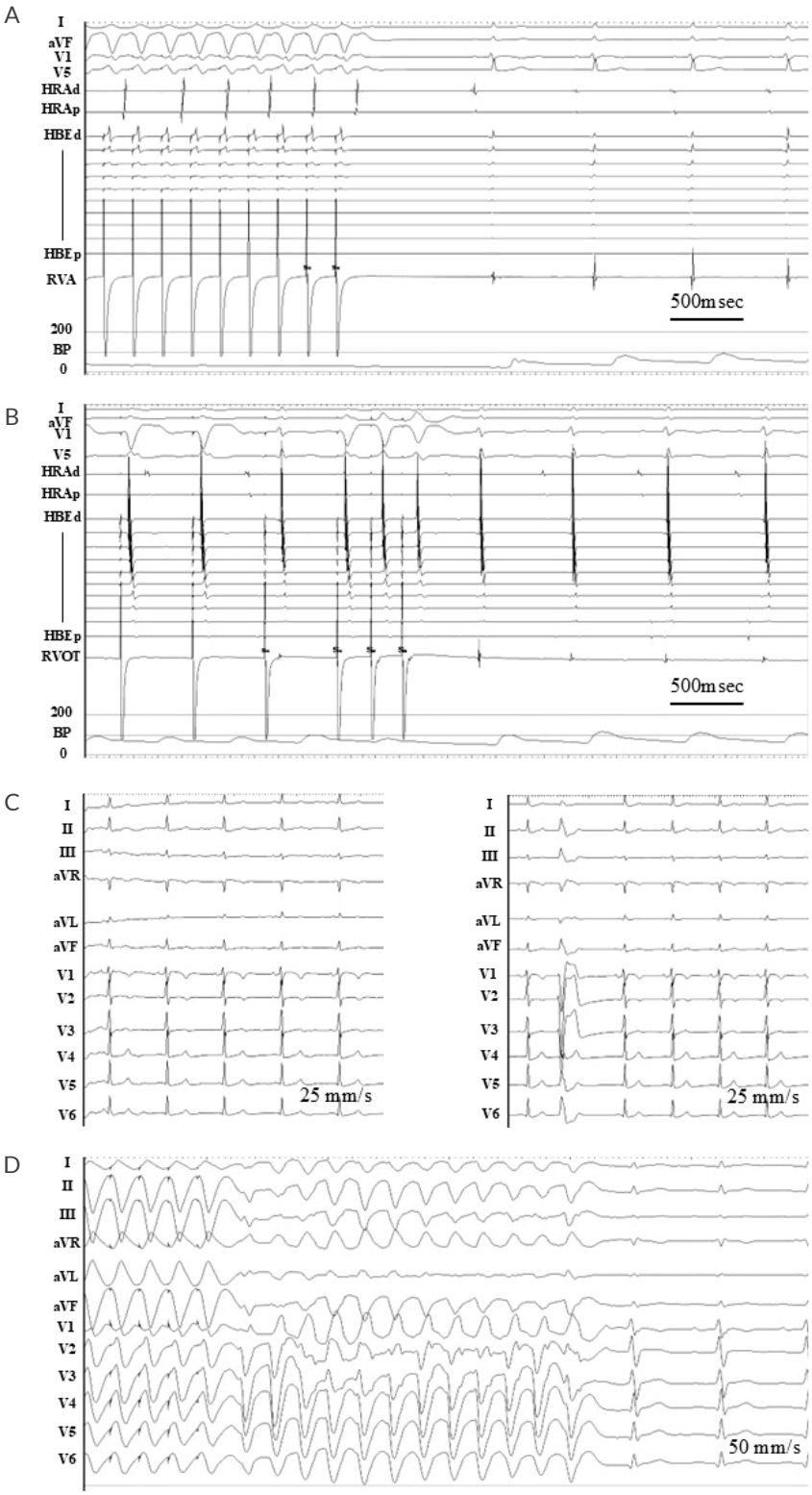

Figure 5. A, B) Programmed electrical ventricular stimulation was performed by applying burst ventricular pacing increasing from 180 to 250 ppm and up to double extra stimuli (the basic cycle length (S1–S1 coupling interval) of 600 ms, and the extra-stimulus pacing with S1–S2 coupling interval of 300–260 ms, S2–S3 coupling interval of 300–160 ms) from the right ventricular (RV) outflow tract and apex, but any ventricular tachycardia (VT) could not be induced; C) Morphologies of 12-lead ECGs before (left) and after (right) a pilsicainide provocation. No remarkable ST-segment elevation in V1, nor changes in QRS morphologies were observed; D) Burst pacing from RV apex at 240 ms following pilsicainide administration induced nonclinical VT that terminated spontaneously.findings then gradually normalised.

ECG findings prior to those provocation[7]. Reportedly, 77% of drug-induced BrS owing to non-cardiac medications occur in men, typically within 72 hours of therapy initiation, and all cases demonstrate a type I Brugada pattern in ECG during treatment[8]. In patients with drug-induced BrS, the median annual rate of life-threatening arrhythmias is 0.5% over 5 years and 0.25% over 10 years, with a mortality rate of 13%[7,8]. Although the mechanism underlying drug-induced BrS remains unclear, latent ion channel dysfunction and pharmacological blockage of depolarising sodium or calcium channels have been suggested as potential mechanisms. Specifically, SCN5A mutation is a predictor of life-threatening clinical events, such as sudden cardiac death, and programmed ventricular stimulation can potentially be utilised for sudden cardiac death risk stratification for asymptomatic patients (either completely asymptomatic or those with vasovagal syncope)[9]. In this case, catheter ablation was initially planned if an electrophysiological examination conducted after discontinuing entrectinib-induced clinical VT. However, clinical VT could not be

induced by any programmed electrical stimulation, leaving the possibility that entrectinib provoked drug-induced BrS resulted in sustained VT. Moreover, two cases of entrectinib-induced BrS have previously been reported[2,3]. In these reports, ventricular arrhythmias appeared three days after entrectinib initiation. However, in our case, VT occurred 12 days after entrectinib initiation.

The estimated prevalence of BrS ranges from 0.02 to 0.1% in Europe and from 0.1 to 0.25% in Asia, with Southeast Asia having the highest prevalence[10]. The pathophysiology of BrS is complex, involving both genetic and pharmacological factors. Patients with drug-induced BrS differ from those with other types of BrS in terms of ethnicity and ventricular fibrillation inducibility rates, making identification of patients at high risk of drug-induced BrS challenging[11]. Our report suggests that continuous ECG monitoring or frequent ECG recording at least once a day several days after entrectinib initiation may help detect entrectinib-induced BrS irrespective of being in or out of hospital. However, our study is limited by the lack of SCN5A gene mutation analysis, as the patient did not provide consent. Further analyses involving a large number of cases are needed to better elucidate the relationship between entrectinib and drug-induced BrS.

CONCLUSION

The relationship between entrectinib and drug-induced BrS remains unclear; reports of entrectinib-induced BrS are rare. Identifying patients at high risk of entrectinib-induced BrS is challenging. Continuous ECG monitoring or frequent ECG recording at least once a day several days following entrectinib initiation may help detect entrectinib-induced BrS, irrespective of being in or out of hospital.

REFERENCES

1. Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, et al. trial investigators. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1–2 trials. *Lancet Oncol* 2020;**21**:261–270. Erratum in: *Lancet Oncol* 2020;**21**:e70. Erratum in: *Lancet Oncol* 2020;**21**:e341.
2. Kubota M, Iso Y, Mori H, Suzuki H. Entrectinib-induced Brugada phenocopy in a patient with metastatic non-small cell lung cancer. *Eur Heart J Case Rep* 2023;**7**:ytad324.
3. Futamura K, Hase T, Tanaka A, Sakai Y, Okachi S, Shibata H, et al. Lethal ventricular arrhythmia due to entrectinib-induced Brugada syndrome: a case report and literature review. *Int Cancer Conf J* 2023;**12**:299–304.
4. Wellens HJ, Bär FW, Lie KI. The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex. *Am J Med* 1978;**64**:27–33.
5. Kindwall KE, Brown J, Josephson ME. Electrocardiographic criteria for ventricular tachycardia in wide complex left bundle branch block morphology tachycardias. *Am J Cardiol* 1988;**61**:1279–1283.
6. Ueoka A, Morita H, Watanabe A, Morimoto Y, Kawada S, Tachibana M, et al. Prognostic significance of the sodium channel blocker test in patients with Brugada syndrome. *J Am Heart Assoc* 2018;**7**:e008617.
7. Tisdale JE, Chung MK, Campbell KB, Hammadah M, Joglar JA, Leclerc J, et al. American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing. Drug-induced arrhythmias: a scientific statement from the American Heart Association. *Circulation* 2020;**142**:e214–e233.
8. Konigstein M, Rosso R, Topaz G, Postema PG, Friedensohn L, Heller K, et al. Drug-induced Brugada syndrome: clinical characteristics and risk factors. *Heart Rhythm* 2016;**13**:1083–1087.
9. Russo V, Caturano A, Migliore F, Guerra F, Francia P, Nesti M, et al. Long-term clinical outcomes of patients with drug-induced type 1 Brugada electrocardiographic pattern: a nationwide cohort registry study. *Heart Rhythm* 2024;**21**:555–561.
10. Nakano Y, Shimizu W. Brugada syndrome as a major cause of sudden cardiac death in Asians. *JACC Asia* 2022;**2**:412–421.
11. Milman A, Sabbag A, Conte G, Postema PG, Andorin A, Gourraud JB, et al. Characteristics of patients with spontaneous versus drug-induced Brugada electrocardiogram: sub-analysis from the SABRUS. *Circ Arrhythm Electrophysiol* 2023;**16**:e011360.