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Case Report

A case of ventricular fibrillation without left ventricular systolic dysfunction induced by trastuzumab emtansine for breast cancer[☆]Morihiro Takeda (MD, PhD)^{*}, Tsuyoshi Takada (MD, PhD), Nobuyuki Shiba (MD, PhD)

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ABSTRACT

Trastuzumab-induced cardiomyopathy is a known complication of its use in breast cancer treatment. However, cardiac complications of trastuzumab without left ventricular systolic dysfunction have been rarely reported. These include left bundle branch block, sinus node dysfunction, and ventricular tachycardia. We herein report a case of a 47-year-old female with human epidermal growth factor receptor 2-positive, stage IV breast cancer without a history of cardiovascular disease. During treatment with trastuzumab emtansine (T-DM1), she presented with out-of-hospital cardiac arrest and was resuscitated by automated cardioverter defibrillator (AED). Emergent cardiac catheterization revealed no organic obstruction and coronary vasospasm in her coronary arteries, and no left ventricular systolic dysfunction. Ventricular fibrillation (VF) was documented by an event memory of AED. T-DM1 was withdrawn and implantable cardioverter defibrillator was implanted. Thereafter, VF or life-threatening arrhythmia were not documented for 36 months until her death by breast cancer. We concluded that the etiology of her VF event was T-DM1-induced cardiotoxicity. We believe this is the first report of life-threatening VF event without cardiomyopathy induced by T-DM1.

<Learning objective: Trastuzumab emtansine (T-DM1) therapy for breast cancer has been associated with an increased risk of left ventricular dysfunction. However, non-myopathic cardiac complications of T-DM1 are rare. To our knowledge, this is the first report that describes a ventricular fibrillation without left ventricular dysfunction after taking T-DM1. We strongly suggest that not only monitoring of left ventricular systolic function, but heart-rhythm monitoring should be performed in patients taking T-DM1.>

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Introduction

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate comprising the anti-human epidermal growth factor receptor 2 (HER2) antibody trastuzumab bound to the anti-microtubule agent emtansine [1]. T-DM1 is taken up by HER2-positive cells and then trastuzumab exhibits its anticancer effects by modulating proliferative signaling cascades, whereas DM1 component inhibits tubulin polymerization and induces cell death in proliferative cells [1]. This targeted immunotherapy has been approved for the treatment of HER2-positive breast cancer. DM1 has a narrow therapeutic window for oncology, but its linkage to trastuzumab, with

an average of 3.5 drug-antibody ratio, selectively targets the cytotoxin to malignant cells that overexpress the HER2 receptor tyrosine kinase, thereby widening its therapeutic window [2]. Clinically, trastuzumab has been shown to be highly efficacious as a single agent for the treatment of breast cancer or in conjunction with anthracyclines. However, it has been associated with numerous cardiotoxic effects. The most common cardiac complication of trastuzumab is cardiomyopathy [3]. However, non-myopathic cardiac complications such as ventricular tachycardia (VT), left bundle branch block, and sinus node dysfunction are being reported due to a significant rise in the use of trastuzumab [4]. We herein report a rare case of a 47-year-old female with breast cancer treated by T-DM1 who experienced cardiopulmonary arrest due to ventricular fibrillation (VF) without left ventricular (LV) systolic dysfunction.

[☆] This is an original manuscript and has not been previously published or submitted to another journal.

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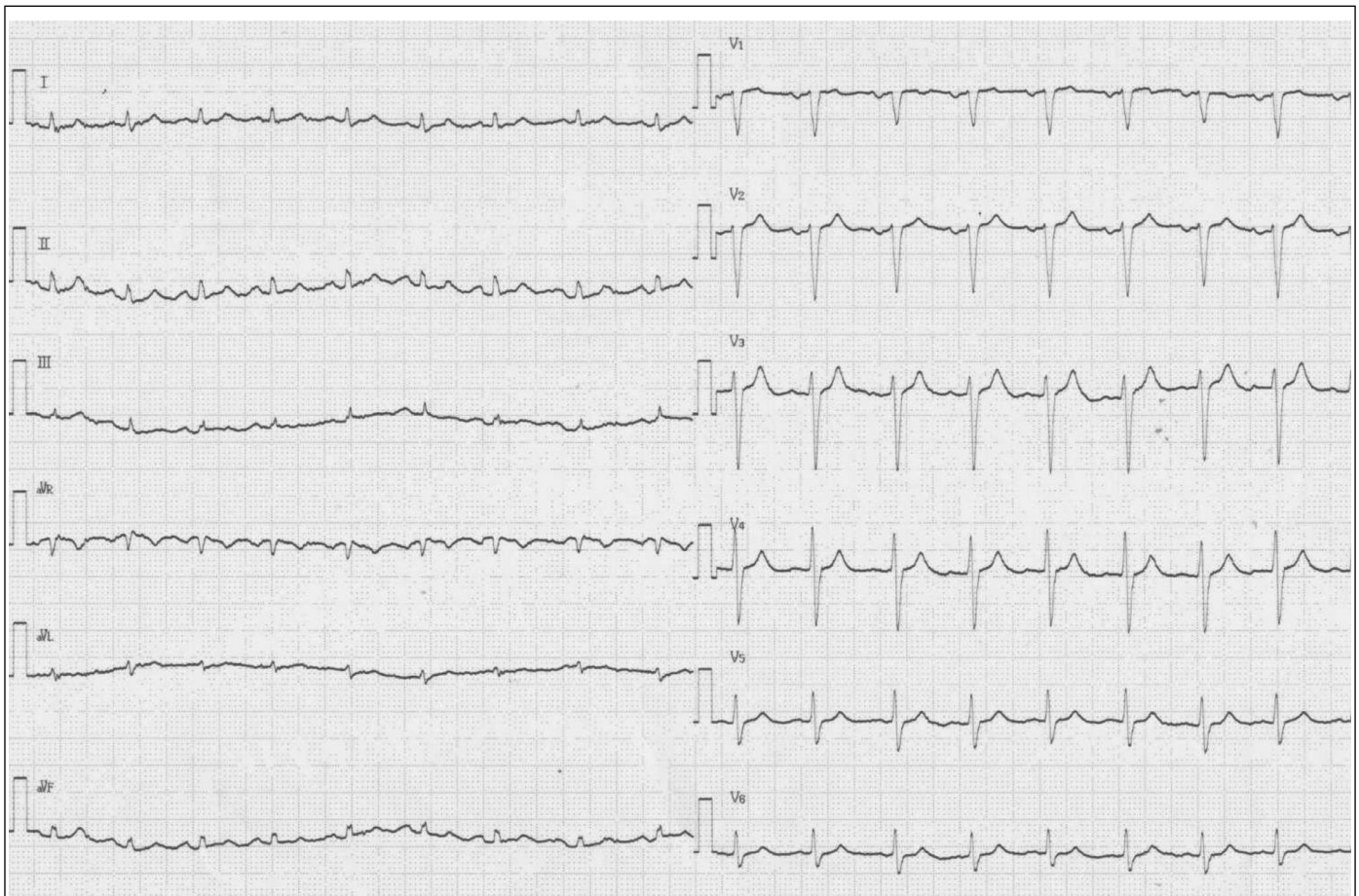
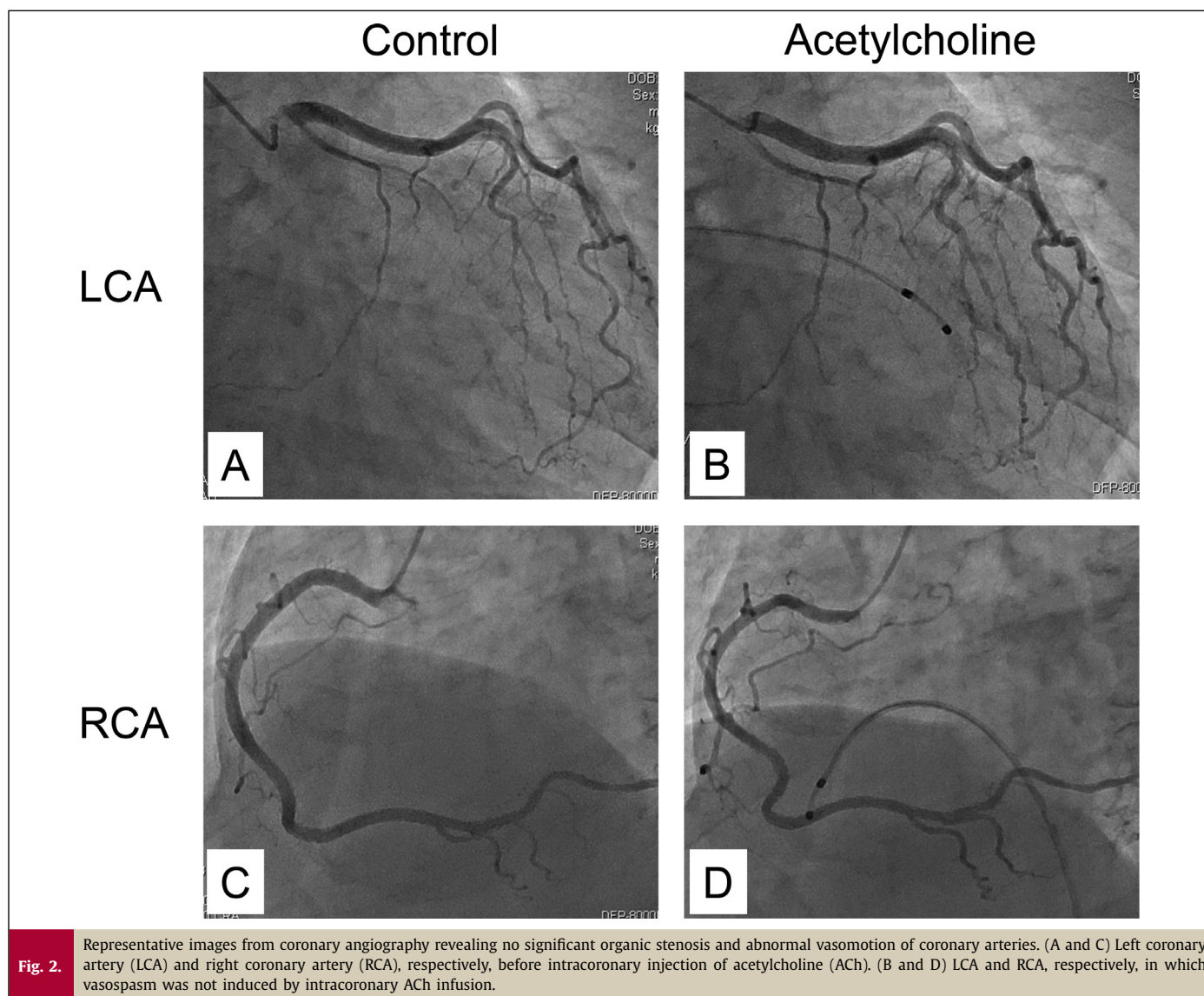


Fig. 1. 12-lead electrocardiogram on admission. It shows normal sinus rhythm, normal conduction and no ischemic changes.

Case report

A 47-year-old female patient was admitted to our hospital because of witnessed cardiopulmonary arrest (CPA). She had no past medical histories prior to the treatment of breast cancer. Before the CPA event, she had undergone chemotherapy for a T4N3M1, stage IV, grade 3, estrogen receptor-positive, progesterone receptor-positive, HER2-positive invasive ductal carcinoma of the right breast for about four years. Her breast cancer was diagnosed as inoperable and then goserelin and tamoxifen treatment were initiated as first-line chemotherapy, concomitantly with palliative radiotherapy for lumbar vertebrae. After 11 months, tamoxifen was replaced by anastrozole because of the significant elevation of serum tumor-marker level. However, five months later, computed tomography revealed multiple liver metastases. Therefore, second-line chemotherapy with trastuzumab and paclitaxel was started and continued for two years with a good response without cardiovascular events. The pre-chemotherapy echocardiogram showed a good LV ejection fraction (EF) of 68%, which was unchanged for two years. However, she had to withhold chemotherapy for about six months because of economic reasons until multiple lung and supraclavicular lymph node metastases were detected during a follow-up visit. Then she received two cycles of T-DM1 treatment at 3.6 mg/kg once every three weeks with minimal toxicity. However, a week after the third treatment of T-DM1, she suddenly developed an out-of-hospital CPA and cardiopulmonary resuscitation was immediately given by bystanders. Automated ex-

ternal defibrillator (AED) detected a shockable rhythm and recommended a shock delivery, which was then administered. When the patient was taken by an ambulance to our hospital, electrocardiogram (ECG) showed normal sinus rhythm and no ST segment and conduction abnormalities (Fig. 1). Echocardiography revealed no abnormalities such as reduced LVEF, significant valvular lesion, signs of right-heart strain, and regional wall motion abnormalities of LV. Emergent coronary angiography revealed no significant stenoses in epicardial coronary arteries (Fig. 2A and C). LVEF measured by left ventriculogram was 77% and no regional wall motion abnormalities were detected. We speculated that the coronary vasospasm might be the possible cause of her CPA and therefore a spasm provocation test using acetylcholine (ACh) was performed simultaneously. ACh 100 µg was infused into the left coronary artery, which did not demonstrate significant vasospasm (Fig. 2B). Thereafter, 50 µg of ACh infusion into the right coronary artery also demonstrated no significant vasospasm (Fig. 2D). During the ACh infusion, the patient did not develop a chest pain and ischemic ECG changes. We kept monitoring her ECG for a week after admission but could not detect any VT or VF events. Cardiac magnetic resonance imaging showed no late gadolinium enhancement in the LV wall, suggesting no significant myocardial fibrosis. However, the ECG recordings obtained from the AED memory apparently showed VF (Fig. 3). Although we did not perform gene analysis for arrhythmia syndromes, we asked the patient and her family and confirmed no family histories of sudden death and hereditary arrhythmia syndromes. Furthermore, the patient had



no symptoms such as chest pain or syncope prior to VF event. No cause of VF could be determined. Therefore, from the clinical course and invasive and non-invasive studies, we concluded that the VF could be attributed to the cardiotoxicity of the T-DM1. Because life-threatening VF event was clearly documented by AED, she underwent implantation of implantable cardioverter defibrillator (ICD) without diagnostic electrophysiological study. During her hospitalization, there were no recurrent arrhythmic events and therefore we did not prescribe anti-arrhythmic drugs. She was discharged with no chest symptoms and chemotherapy using T-DM1 was withdrawn. We followed her at outpatient and her breast cancer was treated by aromatase inhibitor exemestane. She died from advanced breast cancer 36 months after her VF episode. No arrhythmic events except for isolated premature atrial and ventricular contraction were detected by ICD memory during her follow-up period after cessation of T-DM1.

Discussion

In this report, we have presented a rare case of non-cardiomyopathic life-threatening VF in a patient being treated with T-DM1. Although it is impossible to prove that T-DM1 was def-

initely responsible for the VF event, the episode remains unexplained by any other factors. LV systolic dysfunction is a well-documented side effect of trastuzumab [3]. It has been reported that cardiotoxicity occurs in approximately 4% of patients receiving trastuzumab monotherapy and 27% of patients receiving it along with anthracycline and cyclophosphamide [5]. Therefore, it is recommended that the patients taking trastuzumab should be followed by echocardiography. On the other hand, non-myopathic cardiac complications of trastuzumab are either rare or underreported. These include left bundle branch block, sinus node dysfunction and non-sustained VT [4]. These were mostly asymptomatic or eventually resolved with cessation of trastuzumab. In fact, on a pooled analysis of 1961 advanced HER2-positive breast cancer patients receiving T-DM1, 14 cases (0.71%) had unspecified arrhythmias during the treatment but there were no cases of cardiac death reported [6]. However, Oliveira et al. reported the case of sudden death, presumably from arrhythmia, during adjuvant trastuzumab therapy of breast cancer, although the ECG of fatal arrhythmia was not specified [7]. To our knowledge, there have been no reported cases of VF without LV systolic dysfunction after trastuzumab or T-DM1 treatment. In our case, we cannot conclude whether the trastuzumab component was exclusively responsible

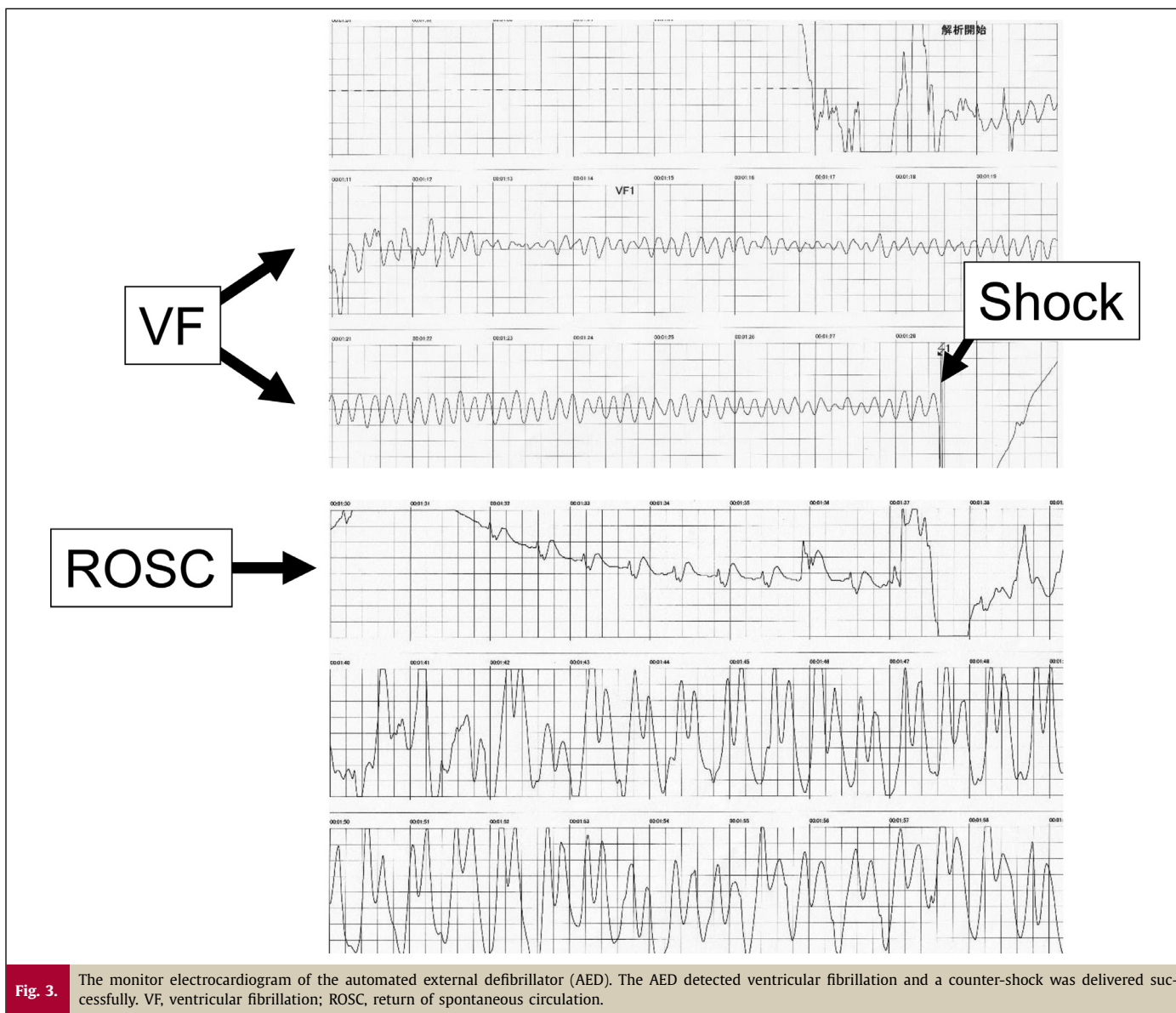


Fig. 3. The monitor electrocardiogram of the automated external defibrillator (AED). The AED detected ventricular fibrillation and a counter-shock was delivered successfully. VF, ventricular fibrillation; ROSC, return of spontaneous circulation.

for the VF event or whether emtansine contributed to it to some level. However, the similarity in terms of clinical course and risk factors between trastuzumab-associated cardiotoxicity and T-DM1-associated cardiotoxicity suggest that it is the trastuzumab component, and not the emtansine component, which is the main driver of cardiotoxicity [6].

The underlying molecular mechanisms of trastuzumab involved in arrhythmogenesis remains unclear, but existing evidence has suggested that accumulation of reactive oxygen species (ROS) resulting from the inhibition of HER2-mediated anti-oxidative action by trastuzumab could play an important role [4]. Multiple cardiac ion channels are redox-regulated and are involved in the arrhythmogenic process under oxidative stress conditions [8]. However, in general, alteration of ionic dynamics solely does not produce VT and VF [9]. Instead, it provides a substrate that when coupled to functional and structural deterioration of cell coupling, such as gap junction remodeling and myocardial fibrosis, promotes triggered activity causing VT and VF [4,9]. Indeed, downregulation of connexin43, the major cardiac gap junction protein, has been reported

in cardiomyocytes subjected to oxidative stress [8,9]. Additionally, it was reported that genetically engineered mice with cardiac-restricted inactivation of connexin43 after birth develop a conduction defect and sudden cardiac death from spontaneous ventricular arrhythmias in the absence of LV dysfunction [10]. Further experimental, clinical, and epidemiological investigations are warranted to elucidate the role of ROS, connexin43, and of any other factors involved in order to identify possible therapeutic target to reduce trastuzumab-induced arrhythmogenesis.

Given the relative novelty of T-DM1 therapy, and the increasing numbers of patients who will be treated with T-DM1 in the future, we should use caution about the risk of cardiac sudden death by VF in patients undergoing treatment with T-DM1, even if there is no LV systolic dysfunction and the patients are asymptomatic. At present, there are no guidelines available for monitoring of arrhythmias in patients taking T-DM1. To predict life-threatening arrhythmic events and protect against sudden cardiac death by them in patients who undergo trastuzumab therapy, we recommend periodic echocardiography for early detection of LV

dysfunction and prophylactic usage of wearable cardioverter defibrillator vest in patients with severe LV dysfunction. However, in our case, the patient had neither LV dysfunction nor symptoms prior to VF. Therefore, it was extremely difficult to predict her VF event. Although implantable loop recorder may be helpful for screening of arrhythmias, this will be overuse of it for all trastuzumab-treated patients. Further studies will be required to identify VF-high-risk group from all trastuzumab-treated patients without LV dysfunction.

Declaration of Competing Interest

The authors declare no conflict of interests.

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None.

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